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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

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THE RADIOLOGICAL APPEARANCES OF THE LUNGS IN HEART DISEASE

BY J. F. GOODWIN AND R. E. STEINER

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THE pulmonary circulation is so intimately related to cardiac function that the heart and lungs must be considered as one unit. Careful study of the radiological appearances of the lungs often yields information of the utmost value in the diagnosis and prognosis of various types of acquired and congenital heart lesions.

Although in this paper the main emphasis will be laid on the radiology of the lungs, this does not imply that the appearance of the heart shadow is not of equal importance.

CONGESTIVE HEART FAILURE

The radiological changes in the lungs are common to all forms of congestive failure irrespective of the cause. Acute left ventricular failure results in pulmonary œdema, the radiological appearances consisting of massive, semi-confluent shadows which radiate from the hilar regions into the peripheral lung fields in the form of " butterfly wings." (Fig. 1.)

The bases, apices and peripheral zones of the lungs are unaffected (Jackson, 1951). The distribution is characteristic and helps to differentiate these opacities from inflammatory lesions. The shadows are usually symmetrical but occasionally can be unilateral or lobar (Hodson, 1950). (Fig. 2.)

The " butterfly shadows " of pulmonary œdema are thought by Herrnheiser and Hinson (1954) to be due to differences between the anatomical arrangement of the pulmonary arteries in the central core and in the peripheral cortex of the lung, but this is only a partial explanation. The shadows may clear within a matter of hours or persist for days or weeks, even though the patient's dyspnœa has improved and the lungs appear to be clear clinically.

The shadows are due to transudations of œdema fluid from the lung capillaries into the alveoli. Usually the fluid is thin and is readily re-absorbed, but sometimes it is thick, gelatinous and fibrinous and can undergo organisation. This can be seen in patients dying of uræmia (Doniach, 1947), or in patients who have had multiple attacks of left ventricular failure due to hypertension

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but whose lives have been prolonged with Methonium compounds (Doniach, Morrison and Steiner, 1954).

Pleural effusions are common in congestive heart failure and in chronic left ventricular insufficiency. They are usually but by no means always bilateral, and left-sided collections are more prominent than right-sided ones. These effusions are associated with cardiac enlargement and some distension of the main pulmonary arteries. The effusions can also be inter-lobar or encysted, and may cause considerable diagnostic difficulty by simulating other pulmonary pathological conditions such as lung abscess or neoplasm, unless they are adequately localised by radiographic means (Stewart, 1928; Kiser, 1929; Stein and Schwedel, 1934; Newman and Jacobson, 1951). Furthermore, effusions may undergo partial organisation which results in pleural thickening, diaphragmatic elevation with distortion of the normal pulmonary pattern, and mediastinal displacement. The gross enlargement of the pulmonary arteries which is seen in certain forms of congenital heart disease, mitral valve disease and pulmonary heart disease does not occur merely as a result of congestive failure.

Careful correlation of the clinical findings with the radiological appearances of both heart shadow and lungs will usually enable the correct diagnosis to be made.

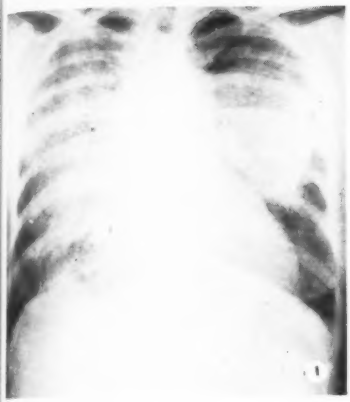
Pulmonary infarction is common in congestive cardiac failure and the radiological appearances will be discussed later in a separate section.

Mitral Valve Disease

The radiological changes in the lungs in mitral stenosis are variable but follow a definite pattern. Enlargement of the main pulmonary arteries has been described by Zdansky (1953), Parkinson (1949), and by numerous other workers. In the past few years considerable attention has been paid to the pulmonary vascular pattern. Goodwin *et al.* (1952) showed by angiographic means that narrowing and irregularity of the small pulmonary arteries at the bases of the lungs was a constant feature in patients with pulmonary hypertension. The extent and severity of these changes is in proportion to the severity of the hypertension. Davies *et al.* (1953) demonstrated that these changes could be detected on plain films and these could be used as a guide to estimate the degree of pulmonary hypertension. (Figs. 3 (*a*) and (*b*).)

Cleland *et al.* (1955) have shown that the severity of the arterial changes reflects the severity of the mitral stenosis and that in some patients regression of the vascular changes may occur after successful valvotomy.

Horizontal lines in the costo-phrenic angles have been described by Kerley (1951) in patients with mitral valve disease. These lines are most often seen in patients with severe pulmonary hypertension due to severe degrees of mitral stenosis (Steiner and Goodwin, 1954; and Short, 1955). (Fig. 4.) They may be transient, vary with attacks of cardiac failure, or become permanent, and they may disappear after successful valvotomy (Cleland *et al.*, 1955). Kerley (1951) and more recently Levine (1955) have suggested that these lines are due to engorged lymphatics, while Fleischner and Reiner (1954) considered them to be produced by deposits of hæmosiderin or œdema in the inter-lobal



1.—Pulmonary œdema. Extensive, bilateral
nt shadows, extending from the hila into the
ral lung fields, leaving relatively clear apical
and lower zones.

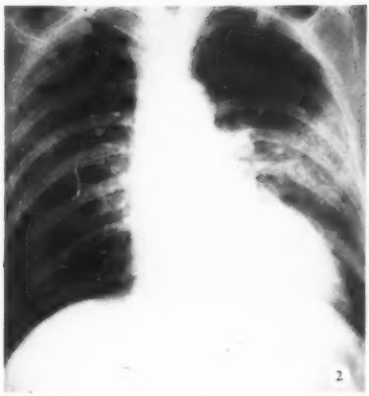
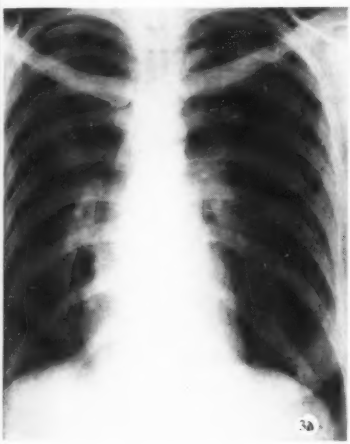


FIG. 2.—Pulmonary œdema, affecting mainly the left mid zone.



a).—Female patient with mitral valve disease.
ulmonary vascular pattern appears normal. The
pulmonary artery is of normal calibre and the
branches diminish equally in calibre in pro-
to the size of the main artery, and can be
into the peripheral lung field. This normal
ary vascular pattern is consistent with a normal
pulmonary artery pressure.

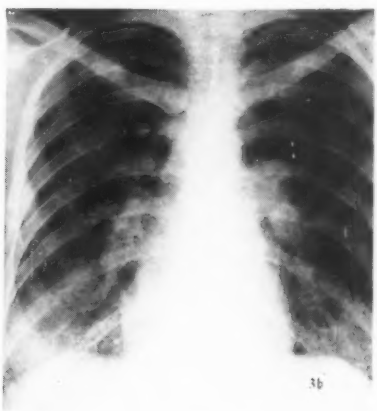


FIG. 3 (*b*).—Same patient, some years later. The main pulmonary artery is now markedly dilated and so are its main branches. The smaller branches, particularly in the mid and lower zones are tortuous narrowed and irregular and cannot be traced accurately into the peripheral lung field. Some of the opacities in the mid and lower zones are non-vascular and are probably due to interstitial fibrosis. These changes are consistent with a marked degree of pulmonary hypertension.

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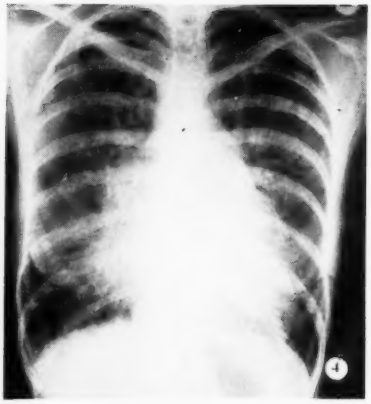


FIG. 4.—Patient with mitral stenosis. The main pulmonary arteries are markedly dilated and the smaller peripheral branches in the mid and lower zones are irregular and narrowed, indicating a raised pulmonary artery tension. Towards the periphery of the lung, a large number of horizontal lines are noted, probably due to distended sub-pleural and pulmonary lymphatics.

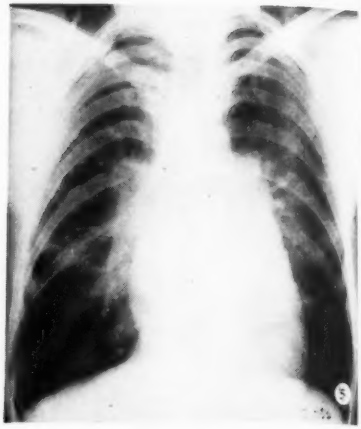


FIG. 5.—Patient with mitral valve disease. A ge
lised, fine stippling is visible in both lung fields d
hæmosiderosis.

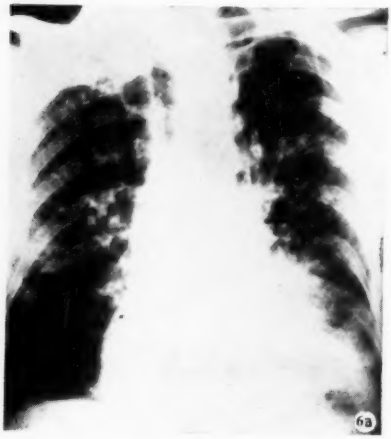


FIG. 6 (*a*).—Patient with chronic bronchitis and emphysema in an acute exacerbation. The heart is enlarged. Very prominent pulmonary arteries with considerable mottling in the left lower zone.

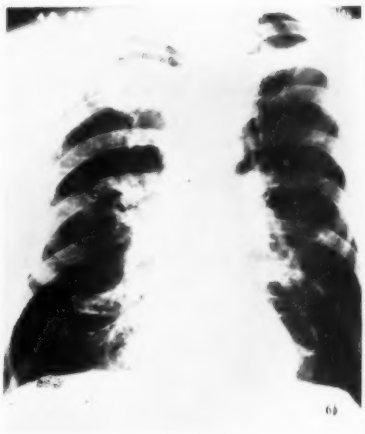
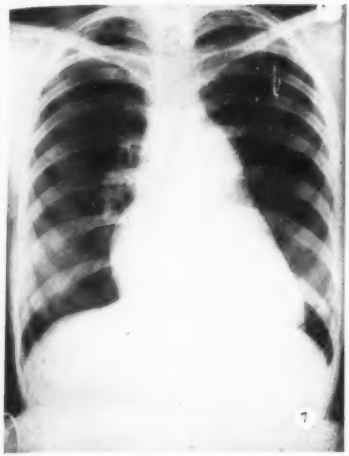


FIG. 6 (*b*).—Same patient, a week later. The hear
regressed to a normal size. The pulmonary art
although still prominent, are smaller and the in
matory changes in the left lower zone have cle



7.—Patient of 34 years with idiopathic pulmonary ertension. There is considerable cardiac enlarge- t involving mainly the right ventricle. Prominent monary artery and prominent main branches which reening showed slight pulsation. The peripheral rial branches are small and constricted and there is siderable under-filling of the lungs.

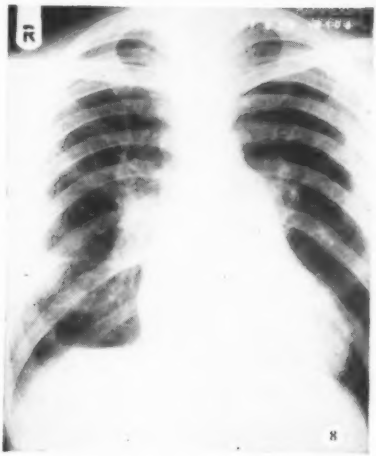
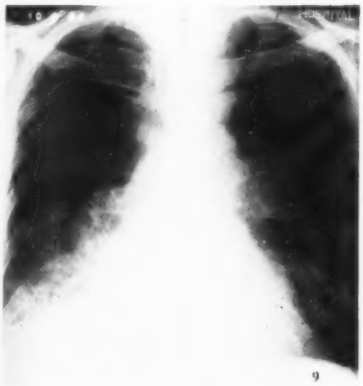


FIG. 8.—A small oval shadow can be seen in the right mid zone towards the peripheral lung field, due to pulmonary infarction.



9.—Massive pulmonary infarction in the right er zone producing extensive consolidation and de- ion of a right lower lobe segment. Note the marked tation of the main lower lobe pulmonary artery.

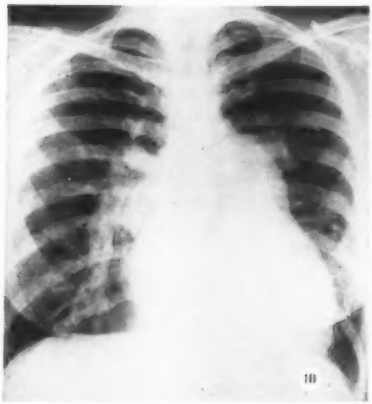


FIG. 10.—Female patient of 32 years, with an atrio septal defect. The heart is enlarged. Very dilated main pulmonary artery and pulmonary artery branches. On fluoroscopy there is intrinsic pulsation of the pulmonary artery which extends well out into the peripheral lung field.

PLATE XVIII

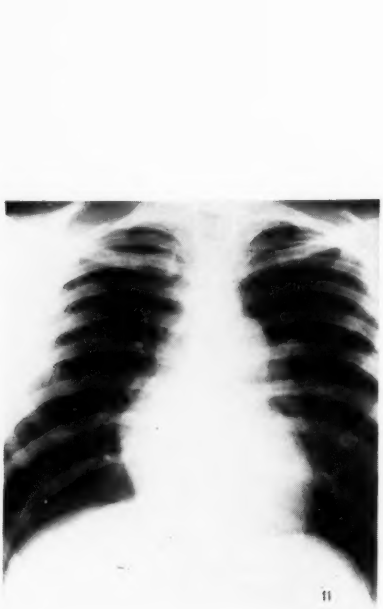


FIG. 11.—Male patient of 16 years with pulmonary stenosis. The heart is slightly enlarged. The main pulmonary artery is dilated. The right and left main and the smaller branches however, are of small calibre and the lung fields are under-filled.

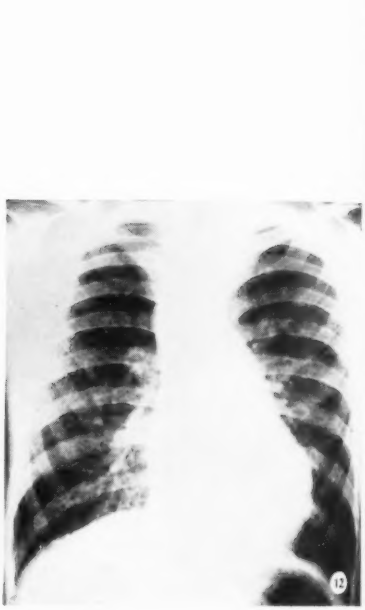


FIG. 12.—Female patient of 6 years with tri atresia. The pulmonary vascular pattern is not distinguishable but in its place there is consid mottling due to bronchial arteries.

septa. Furthermore, Gough (1955) obtained lung sections which showed œdema of the inter-lobal septa together with marked lymphatic distension in the distribution of the lines seen on the radiographs. (Fig. 5.)

Fine, nodular stippling is frequently seen in the lung fields in mitral stenosis. Lendrum *et al.* (1950) showed that these shadows were aggregates of hæmosiderin around the bronchopulmonary capillary anastomoses, and believed them to be due to multiple intra-pulmonary hæmorrhages. Gumpert (1947) and Ellman and Gee (1951) thought that œdema and venous congestion caused lymphatic obstruction, which prevented the removal of the products of hæmorrhage, which became aggregated in radiologically detectable nodules. The severity of these shadows may vary from a generalised "snowstorm" pattern resembling miliary tuberculosis (Gumpert, 1947) to a faint reticulation. Although hæmosiderosis undoubtedly occurs in association with pulmonary hypertension in mitral stenosis, there is some doubt as to the significance of this association (Wood, 1954). Very rarely, nodules due to true bone formation may appear in the lungs (Elkeles, 1947; Steiner and Goodwin, 1954). In addition to these distinctive vascular and nodular changes in the lungs, a diffuse haze and loss of translucency is often present. The nature of this haziness is uncertain. It is not venous or arterial (Davies *et al.*, 1953), but may be due to interstitial transudation of œdema fluid which becomes organised and produces interstitial fibrosis.

Pulmonary œdema occurs not infrequently in mitral stenosis and differs in no way radiologically from that due to left ventricular failure.

Pulmonary Heart Disease

Pulmonary heart disease can be acute, subacute or chronic (Wood, 1950). The former is typified by acute massive pulmonary embolism. The chronic type may be obstructive, due to arteriolar obstruction by multiple small emboli or by various forms of arteritis or carcinomatous infiltration, or anoxic, due to lung disease which interferes with pulmonary function. The most important condition in this latter group is chronic bronchitis and emphysema. Bronchiectasis, chronic tuberculosis, pneumoconiosis, various specific types of pulmonary fibrosis such as scleroderma, sarcoidosis and chest deformities such as severe kypho-scoliosis are less frequent causes of pulmonary heart disease.

The radiological appearances of the lungs depend largely on the underlying pulmonary disease, but in addition to this, characteristic changes are found in the heart and pulmonary arteries. There is evidence of right ventricular and sometimes right auricular enlargement, together with varying degrees of enlargement of the main pulmonary artery and dilatation of its major branches. Right ventricular enlargement and pulmonary artery dilatation are more pronounced in the acute phase, such as occurs in acute exacerbations of chronic bronchitis, when pulmonary hypertension and congestive heart failure are often a feature (Mounsey *et al.*, 1952). (Fig. 6 (*a*) and (*b*).)

In the obstructive type, dilatation of the main pulmonary artery and its major branches can be very marked, while the peripheral lung fields appear under-filled. In such cases pulmonary arterial pressure is considerably elevated and on fluoroscopy, intrinsic pulmonary artery pulsation may be noted,

although this does not extend to the medium-sized branches as in cases of congenital heart disease with a left to right intra-cardiac shunt which causes an increase in pulmonary blood flow.

The condition known as primary or idiopathic pulmonary hypertension is caused by narrowing of the small pulmonary arteries or arterioles, and produces a similar clinical and radiological picture. (Fig. 7.)

Pulmonary Thrombosis and Infarction

Pulmonary infarction is not uncommon in heart disease, especially in patients with chronic congestive failure or mitral stenosis. The radiological appearances of infarction are variable and the classical picture of a wedge-shaped area of consolidation in the peripheral lung fields is not often seen (Hampton and Castleman, 1940). (Fig. 8.) Infarcts may be multiple and resemble inflammatory consolidation, segmental pulmonary deflation, or peripheral pulmonary neoplasm. (Fig. 9.) The radiological appearances frequently lag behind the clinical incident. Large infarcts are often followed by pleural effusions, and a persistent effusion of obscure origin can be due to pulmonary infarction. The right lung is more often involved than the left and the lower lobes are more frequently affected than the upper (Short, 1951).

Recurrent pulmonary emboli can give rise to extensive thromboses of the main pulmonary artery (Owen *et al.*, 1953). This should be suspected radiologically if the right ventricle and main pulmonary arteries are enlarged, with relative under-filling of the peripheral lung fields, and the pulsations of the pulmonary artery are slight or absent. Radiologically demonstrable infarcts may or may not be present. Although pulmonary arterial thrombosis is usually due to pulmonary emboli, primary thrombosis *in situ* has been shown to occur, especially where there is local disease of the pulmonary arteries, as in mitral stenosis (Ball *et al.*, 1955).

Congenital Heart Disease

In congenital heart disease the pulmonary appearances are largely governed by the presence or absence of an intra-cardiac shunt, or of obstruction to the right ventricular outflow pathway or pulmonary artery.

Cases are best divided into two groups, the first with increased pulmonary blood flow due to a left to right intra-cardiac shunt, and the second with a reduced pulmonary flow due to pulmonary stenosis or atresia. In many instances in the second group, such as the Tetralogy of Fallot, there is right to left shunt. The following table classifies the more common congenital anomalies into these two groups.

The appearances of the lungs are very similar in all cases in the first group and consist mainly of a markedly dilated main pulmonary artery and main branches, all of which exhibit definite intrinsic pulsations on fluoroscopy, which can also be seen in the medium-sized vessels when viewed " end-on " with a small screening aperture. (Fig. 10.) In the absence of a left to right shunt, this pulsation in the medium-sized vessels is not visible. In cases in which severe pulmonary hypertension due to an increased arteriolar resistance develops, the shunt may become balanced or reversed, in which case the intrinsic pulsation

TABLE I.—CONGENITAL ANOMALIES OF THE HEART

With over-filled lungs. (Left to right shunt)

Diagnosis	*The radiological appearances of the lungs*	*The radiological appearances of the heart*
Patent ductus arteriosus	Large pulmonary arteries. Hilar dance	L.A.+L.V.+ (R.V.+)Aorta+
Atrio septal defect ..	Large pulmonary arteries. Hilar dance	R.A.+ R.V.+ Small aorta.
Ventricular septal defect (large)	Large pulmonary arteries. Hilar dance	(R.V.+) L.V.+ (L.A.+)
Eisenmenger's Complex*	Large pulmonary arteries Hilar dance	R.V.+ R.A.+ (L.V.+)
Complete transposition of pulmonary artery and aorta†	Large pulmonary arteries. Hilar dance	R.V.++ Often anomalous position of systemic outflow pathway, which occupies the usual position of the pulmonary artery (Goodwin *et al.*, 1953)
Anomalous pulmonary venous drainage (total or partial)	Large pulmonary arteries. Hilar dance	May be characteristic " figure of 8 " cardiac contour due to double superior vena cava (Snellen and Albers), 1952

* Eisenmenger Complex here denotes a ventricular septal defect with a bi-directional shunt and pulmonary hypertension.

† Occasionally, complete transposition will be associated with underfilled lungs, as when pulmonary stenosis is also present.

With normal or under-filled lungs. (Including cases with right to left shunt)

Diagnosis	*The radiological appearances of the lungs*	*The radiological appearances of the heart*
Small ventricular septal defect (maladie de Roger)	Normal	Normal
Valvular pulmonary stenosis with or without patent foramen ovale	Main pulmonary artery enlarged. Under-filled lungs	R.V.+ R.A.+
Tetralogy of Fallot ..	Under-filled lungs. Main pulmonary artery enlarged if stenosis valvular	R.V.+ (20% abnormal position of aortic arch)
Tricuspid atresia ..	Under-filled lungs. Small pulmonary artery. Bronchial artery shadows	R.V. small or absent. L.V.+ (R.A.+)
Ebstein's disease of the tricuspid valve	Normal or under-filled lungs. Pulmonary artery small	R.A.++ R.V. small
Pulmonary atresia	No visible pulmonary artery. Bronchial arteries	R.V.+
Persistent truncus arteriosus‡	Under-filled lungs. Bronchial arteries. Abnormal small " pulmonary " arteries arising from a common arterial trunk	Often anomalous position of common trunk which occupies position of the pulmonary artery (Goodwin *et al.*, 1953)

‡ Cases of persistent truncus arteriosus may have large " pulmonary " arteries arising from a common trunk and well-filled lungs.

in the medium-sized pulmonary arteries disappears and the peripheral lung fields appear less vascular. The horizontal basal striations and basal congestive shadows seen in mitral stenosis are not present.

The radiological appearances of the lungs in the second group are those of under-filling of the lung fields, except in mild cases where the pulmonary vascular pattern may be normal. For instance, in severe pulmonary stenosis, angiocardiography clearly demonstrates the marked reduction in the calibre of the small pulmonary branches. When pulmonary stenosis is valvular, as is usually the case when the lesion is isolated, post-stenotic dilatation of the main pulmonary artery is the rule and quite vigorous pulsation can be seen in this dilated pulmonary artery segment. (Fig. 11.) When infundibular stenosis is present, the main pulmonary artery is usually small. Valvular stenosis must be differentiated radiologically from conditions in the first group, such as patent ductus arteriosus in which the pulmonary artery enlargement affects both the right and left main branches, and intrinsic pulsation can be seen in the medium-sized arteries; and from cases with severe pulmonary hypertension in which both the right and left main pulmonary arteries are also enlarged.

In cases associated with pulmonary atresia or persistent truncus arteriosus, an exuberant bronchial circulation develops which presents a characteristic radiological appearance, consisting of a nodular vascular pattern around the hilum, apparently replacing the normal linear vascular pattern. (Fig. 12.) In some instances a large, single bronchial artery may be seen to arise from the aorta, well above the normal hilar position (Campbell and Gardner, 1950; Goodwin *et al.*, 1953).

From the preceding discussion and description of the pulmonary vascular pattern in heart disease, it will be apparent that a complete radiological assessment of the heart and lungs will play a vital part in the diagnosis and prognosis of acquired and congenital heart lesions.

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RADIOTHERAPY IN INTRATHORACIC DISEASE

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1. Methods of Radiotherapy

For practical purposes only two methods of radiotherapy need be considered, namely deep X-ray and megavoltage therapy. The latter can be carried out either by electrically generated megavoltage X-rays or by telecurie therapy as with the cobalt bomb (equivalent to 3 million volts). There is no essential difference in the action of the radiations in these two methods, except insofar as concerns the skin. Owing to the peculiar characteristics of the absorption-curve at equivalent voltages of 2 million and over, the skin dosage is relatively greatly reduced, with correspondingly less discomfort to the patient following treatment. On the other hand, the effect of the radiations on the growth cells is identical, and there is little or nothing that can be achieved by supervoltage therapy with the methods at present available which cannot be achieved by careful planning and treatment-application at deep-therapy voltages. Nevertheless, because of the greater penetrating power of the megavoltage radiations, where high-dose localised irradiation is indicated this can be obtained with greater ease both in planning and execution by their use. Where the indication is for wider, more regional irradiation, on the other hand, the local dosage is lower and the technique less exacting, so that there is no advantage gained from megavoltage therapy.

2. Carcinoma of the Lung

Radiotherapy in carcinoma of the lung is usually considered under two headings, namely radical and palliative. In the radical treatment, a circumscribed growth is taken up to strictly localised very high dosage in the dual hope that the growth may be destroyed and that no metastases exist. In the palliative group a wider region is exposed to the radiations with necessarily reduced dosage, in the hope that growth will be restrained, or local masses which are causing pressure effects will be reduced or will disappear. Radical radiotherapy is carried out by high-voltage X-rays or megavoltage therapy (*i.e.*, supervoltage X-rays or telecurie therapy). Palliative treatment is carried out by high-voltage X-rays.

Radical Radiotherapy

Radical irradiation entails an intensive daily course of treatment extending over a period of from four to six weeks. There is considerable constitutional reaction and the risk of damage to structures in the neighbourhood of the growth is far from negligible. Moreover, it is likely that where the treatment

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fails to control the disease, by reason of the severe damage to the tumour bed, and the destruction of its resistance to the growth, life may actually be shortened. Clearly, this is not a treatment to be undertaken without reasonable hope of corresponding benefit. Is this hope in fact afforded by radical radiotherapy in carcinoma of the lung?

It cannot be denied that the results of this form of treatment of lung cancer are miserably disappointing. In the Survey of Cancer in London published by the British Empire Cancer Campaign in 1952, an analysis was made of the results in 200 cases of lung cancer treated by high-voltage X-rays alone in various London hospitals. Only 3 patients survived five years, in none of whom had there been a biopsy, while no fewer than 34 patients were recorded as having died from the effects of the treatment. The proportion of cases treated by radical methods is not stated, but from the high treatment mortality-rate it seems probable that at least a considerable number must have been submitted to radical treatment. Among the best survival figures so far recorded are those of Gwen Hilton (1955), who reported 8 patients (4 with histological confirmation of the diagnosis) of a carefully selected 203 submitted to radical treatment, who survived five years. At the Christie Hospital, Manchester (1955), 7 patients of a total of 254 treated survived five years. Other statistics (Dobbie, 1944, and Shorvon, 1947) have given five-year survival rates from 0 to 2 per cent. The conclusion seems inescapable that radical radiotherapy can only be justified, if at all, in very stringently selected cases. What should be the criteria of selection?

The position must be faced that there is simply no method of ensuring that in any given case the disease is, in fact, circumscribed, and that early metastasis has not taken place. However, experience shows that the likelihood of both early local spread and metastasis is much greater in oat-celled carcinoma and other undifferentiated growths than, say, in a keratinising squamous-celled carcinoma. If the biopsy reports, where they exist, in the rare five-year survivals reported from various sources, are considered, it will be found that nearly all are squamous-celled carcinoma. It seems to follow that small as are the prospects of long date survival in squamous-celled carcinoma with radical radiotherapy, they are infinitesimal in the oat-celled group. In the B.E.C.C. Survey there were 198 cases of oat-celled carcinoma of the lung and 20 undifferentiated squamous-celled carcinomas, compared with 138 differentiated squamous-celled carcinomas of which 108 were keratinising. In London, at any rate, the undifferentiated growths appeared to be far more common than the differentiated squamous-celled growths, and it is submitted that if oat-celled or undifferentiated carcinoma were regarded as contra-indicating radical radiotherapy the results in the treated cases might be appreciably improved.

This is not the place for discussion of radiotherapeutic technique. However, a further argument against the concentration of very high dosage on very small volumes, even in the treatment of the comparatively early cases, is the observation of Price Thomas (1948), who found that even in the early circumscribed growths the intrapulmonary lymph nodes at either bronchial bifurcation can often be seen to be enlarged at some little distance from the margin of the lesion. These nodes " act as a net to catch migrating cancer cells." Radiotherapy should therefore be planned sufficiently widely to include them.

Even with full exploitation of all modern means of demonstrating the extent of the disease, there will always be a considerable proportion of cases in which either local extensive involvement or remote metastases, or both, will be missed. In selecting cases for radical therapy, therefore, greater reliance must be placed upon clinical judgment than in most other regions. For example, a patient with an apparently localised bronchial growth with no lymph-node involvement and no evidence of metastases may give a history of having felt progressively more ill for some time and of having lost much weight, say a stone. Now, carcinoma of the bronchus is not of itself a particularly toxic condition, although in the late stages cachexia may arise from secondary effects and metastases. Certainly, a localised primary growth with nothing more would be insufficient to account for a marked deterioration in general condition and loss of weight amounting to one stone. In the absence of some satisfactory explanation, therefore, a history of deterioration of this extent raises such a strong suspicion of the presence of secondary deposits that radical irradiation had better not be attempted in such a case. So, also, severe and persistent backache which cannot be explained on other grounds usually turns out to be due to secondaries either in the spine or in the liver. It is not generally recognised how closely secondaries in the liver may simulate lower dorsal secondaries in the spine in the type and distribution of pain. It may be of interest here also to note that in the writer's experience one of the most valuable signs of liver involvement is persistent and otherwise unexplained thirst.

Other contraindications to radical irradiation are persistent tachycardia, which may be due to an early mediastinitis or sometimes to actual involvement of the heart muscle in growth, and unexplained pyrexia which again may be a sign of hepatic involvement although it can, of course, be due to damming up of secretions behind the bronchial obstruction.

The contraindications to radical irradiation may therefore be summarised as follows:

1. Oat-celled carcinoma and other undifferentiated growths.
2. Deterioration in general condition out of proportion to the strictly localised growth.
3. Unexplained pyrexia.
4. Persistent unexplained tachycardia.
5. Severe persistent and unexplained thirst.

Palliative Radiotherapy

In considering whether palliative radiotherapy of a malignant growth should be undertaken it must constantly be borne in mind that there is a " debit side " of the radiotherapy account. The patient either must be taken from his home and put into a hospital or nursing home or he must be prepared to make repeated daily journeys to the place of treatment; and even with the most careful handling some constitutional effect of the treatment is inevitable. The likelihood of benefit and its degree must therefore be carefully weighed against these disadvantages.

It may be said at once that where there is threatened or actual mediastinal obstruction; where there is persistent hæmoptysis; and, in certain cases, where

pain is a marked feature, treatment is usually well worth while. More difficult, however, are the cases in which a carcinoma of the lung has been discovered in a patient who is still fit and without symptoms. In such a case, if the growth is still circumscribed, but is for some technical reason, or on constitutional grounds, inoperable, radical treatment should be considered. Where, however, the disease is too extensive for radical treatment, should palliative treatment be undertaken of a patient in whom there is, as yet, nothing to palliate? This is always a difficult question to decide. In the writer's view, whenever the lung base is involved treatment should not be undertaken. Secondary deposits in the liver are so common in patients with disease in the neighbourhood of the diaphragm that on balance harm is done by attempts at treatment, for patients with hepatic deposits always tolerate radiotherapy badly. Indeed, a patient who suffers undue constitutional effects, nausea, vomiting and especially persistent thirst, should always be suspected of liver deposits and re-investigated accordingly.

It will be clear that the decision whether to treat by radiation any case of carcinoma of the lung is one which has to be considered carefully in every individual case. A list of contraindications to radiotherapy is often given; but the call for relief of a symptom or symptoms may be so urgent that palliative treatment—*e.g.*, of mediastinal obstruction—may be indicated even in the presence of generalised secondary deposits. However, apart from such an urgent indication a large pleural effusion which rapidly re-forms after tapping is a contraindication, as, of course, also disease which is too extensive to offer any hope of being covered with useful dosage. Finally, infection, whether septic or active tuberculous, is a contraindication to radiotherapy.

Cortisone and ACTH

It has been seen that the main obstacles to success in the irradiation of the limited carcinoma of the lung is the damage sustained by the tumour bed in the effort to irradiate it to the requisite high dose level. It has been found that radiation damage to the lung can be controlled, at least in a proportion of cases, by cortisone (Whitfield, Bond and Melville Arnott, 1954). These substances may accordingly prove to have a place in the treatment of carcinoma of the lung by mitigating the effects of the high radiation dosage from which, undoubtedly, many patients are lost within a few months of the treatment. Many factors remain to be elucidated. Perhaps the most important of these is the most advantageous time at which to administer the cortisone. In considering this the presence or absence of infection must play an important part, since the administration of cortisone where infection is present may do harm rather than good. It has to be borne in mind that infection plays a much greater part in the natural history of carcinoma of the bronchus than is often indicated by the temperature chart. Moreover, the infective processes are exacerbated temporarily by the administration of the radiotherapy. It therefore seems undesirable to administer the cortisone or ACTH during the actual treatment or while the reactions consequent upon it are in progress. It may well be that the best time for the administration is three or four months after the treatment, in selected cases in which clinical and radiographic evidence of the

growth has disappeared. It seems likely from work already published (*supra*) that at this stage lung damage already evident is reversible, and it is therefore likely that lung damage which has not already appeared may be warded off. In one case treated by the author for carcinoma of the bronchus severe symptoms attributable to lung damage about nine months after the completion of the irradiation were remarkably relieved by cortisone and the radiographic changes greatly improved, although it is probable that the disease had not been eradicated. It would appear that a good case exists for the trial of cortisone or ACTH in association with radiotherapy in a planned series of cases.

Secondary Deposits

Radiotherapy is of much palliative value in two types of secondary deposit —namely, those in bone, which may cause great pain, and which may be relieved very quickly by irradiation; and cerebral deposits, which can usually be made to disappear by adequate treatment, with relief of raised intracranial pressure and paralysis.

One of the most important rôles of radiotherapy in palliation is in the treatment of rib secondaries. Radiography is not a dependable means of defining the extent of secondaries in ribs but these can be mapped out with considerable accuracy by digital exploration with firm pressure along the course of each rib. The writer uses a single-dose method for the irradiation of rib secondary deposits of limited extent, and relief is usually dramatic even when there has been a pathological fracture. A number of deposits can often be effectively treated at a single visit.

3. Mediastinal Growths

Although the diagnosis of a primary mediastinal growth from carcinoma of the bronchus is sometimes difficult, the radiotherapy of mediastinal growths is carried out on very different principles from those which apply—or have hitherto been applied—to carcinoma of the lung. While in the treatment of carcinoma of the lung the tendency has been to limit the volume irradiated as far as possible, nothing is more certain than that a mediastinal growth which is not treated generously widely will recur early, if it can be made to disappear at all (Fig. 3). There is indeed much in common in the behaviour of the mesoblastic mediastinal growths and oat-celled carcinoma, although the outlook for long-date survival is appreciably better in primary mediastinal growths (9 per cent. five-year survival in the Christie Hospital series). Three, four and five-year survivals are not uncommon even in cases in which the disease is extensive, and results may occasionally be achieved even when the disease affects the upper abdomen as well as the chest (Fig. 4). These growths are mostly reticulo-endothelial in origin, and, to offer the best prospect of benefit, the whole mediastinal lymph-node system must be irradiated, from the level of the second to the level of the ninth or tenth dorsal vertebræ, and treatment carried far enough laterally to allow a margin of healthy tissue *not less* than 2·5 cm. outside the margin of the growth shadow. If the growth is very extensive, or if, in addition, axillary and supraclavicular nodes are involved, and especially if there is hepatic involvement in lymphosarcoma or in Hodgkin's

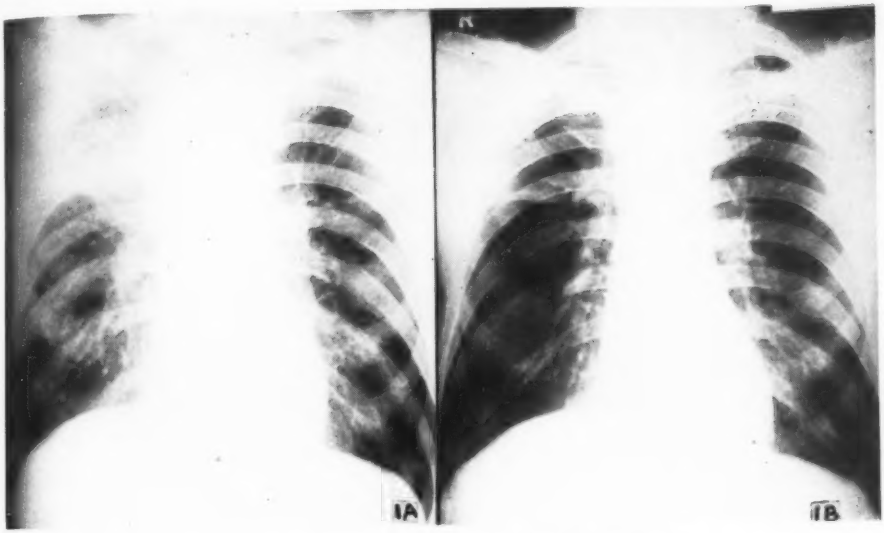

FIG. 1.—Carcinoma of bronchus. Large-field palliative radiotherapy: A. Before, and B. two months after, treatment.

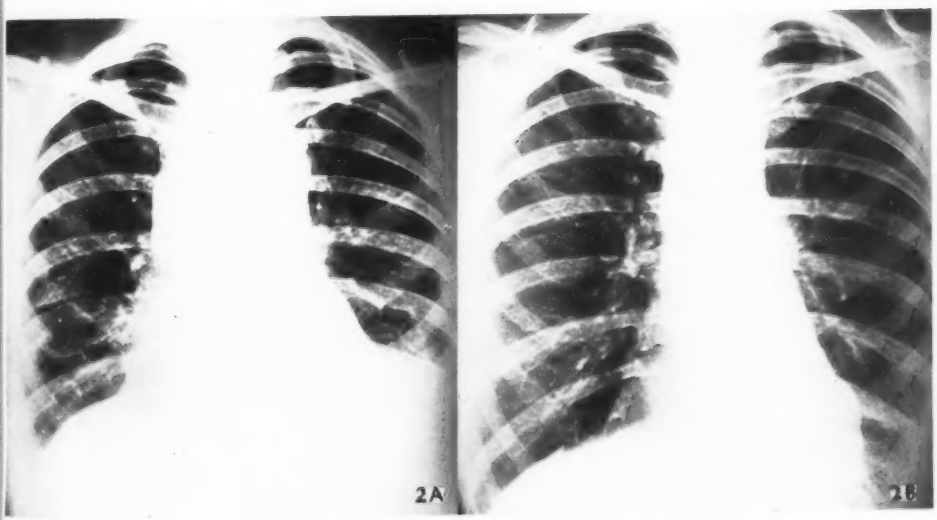

FIG. 2.—Mediastinal tumour treated by deep X-ray therapy—limited fields. Only the bare tumour was irradiated with little margin of surrounding tissue. The disease recurred at the margin of the treated area two months later.

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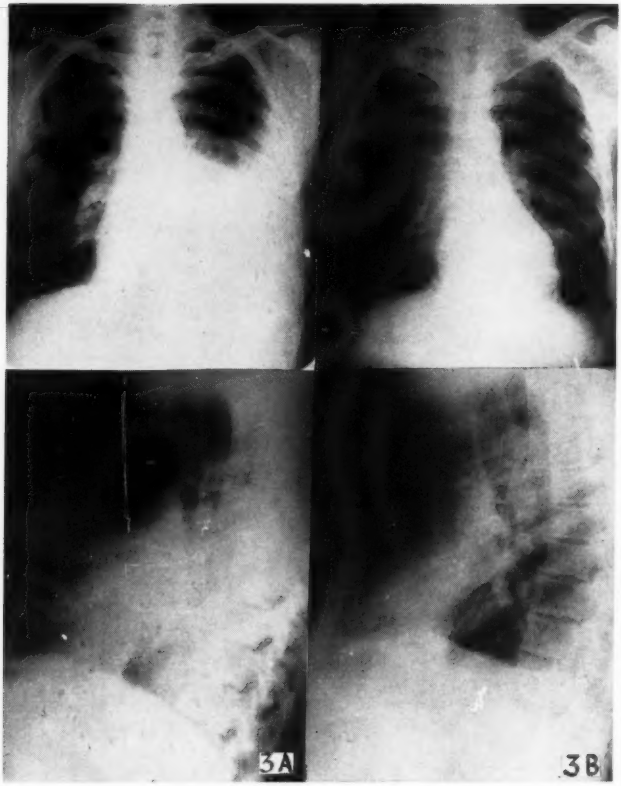

FIG. 3.—Lymphosarcoma chest and upper abdomen bath irradiation. A. Before treatment, and B. Five years after treatment (April 1955).

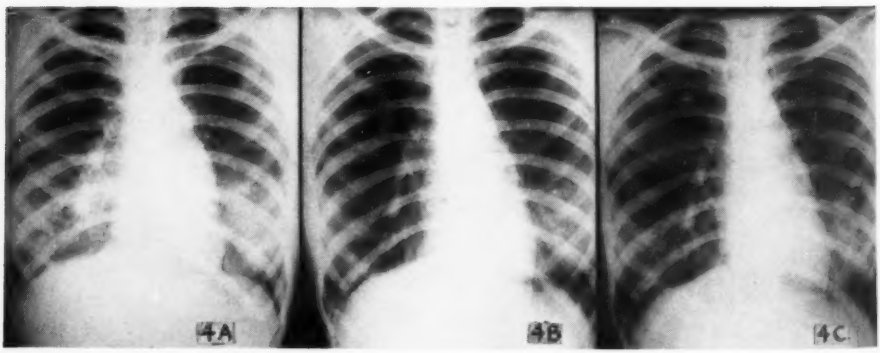

FIG. 4.—Generalised lung deposits in Hodgkin's disease. A. Before, B. In course of, and C. After, bath irradiation.

disease, the only possible method of treatment is the author's bath method (Levitt, 1955). The patient whose skiagrams are shown in Fig. 3 was treated in this way.

The subjective constitutional effects of wide-field irradiation are, if anything, less than those of localised high-dosage irradiation and the risks much less. However, careful blood-count control is necessary throughout the course if the treatment is to be carried through safely.

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EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF BRONCHOGENIC CARCINOMA

(A CRITICAL REVIEW OF THE LITERATURE)

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During the last seven years many reports regarding the value of exfoliative cytology in the diagnosis of bronchogenic carcinoma have appeared in the world medical literature. It is the purpose of this paper to evaluate, in the light of some of these reports, the place of cytology in the diagnosis of bronchogenic carcinoma and to discuss the contribution of the cytologic method towards the early and, therefore, effective treatment of this condition.

It is appropriate to comment briefly on the clinical importance of bronchogenic carcinoma and to point out the limitations of the older methods used for the diagnosis of this condition.

Graham (1935) estimated that bronchogenic carcinoma accounted for only 0·54 per cent. of all malignancies found at autopsy in the United States in 1895. In Ochsner's (1952) series of cases the corresponding figures were 1·1 per cent. and 8·3 per cent. in 1920 and 1938, respectively. Other figures show that the number of fatalities from lung cancer was 6,732 in 1938 as compared with 19,450 in 1948—a 144 per cent. numerical increase in a period of ten years (Ochsner, 1954). In Rosahn's (1940) figures lung cancer accounted for 11 per cent. of all deaths from malignant disease at the Boston City Hospital during the years 1928-1937. As compared with Graham's figure for 1895 this is an almost twenty-fold increase. Of all cancers in the male, lung cancer is now considered to be only second in frequency to carcinomas of the stomach and large bowel (Arkin and Wagner, 1936; Jaffe, 1935; Peerone and Levinson, 1942). Further, as a cause of death in males of the cancer age group, it ranks second only to cancer of the stomach (McKay *et al.*, 1948).

When Graham and Singer (1933) reported the first successsful pneumonectomy, great hopes were entertained about the effective treatment of lung cancer. Modern surgical techniques with the advances in anæsthesiology, antibiotic therapy and increased knowledge of metabolic processes have all tended to decrease operative risks.

However, the "five-year cure" rates are still low. Ochsner and others reported a five-year survival in only 8 per cent. of all their cases in 1947 and only 6 per cent. in 1952.

It would appear that surgery is undertaken too late in the majority of cases —at least several months after the initial symptoms have developed. It is well known that the early symptoms and signs of bronchogenic cancer are quite non-specific. Therefore, until recently, clinicians have depended mostly

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on radiology, bronchoscopy and biopsy or an exploratory thoracotomy to elicit a diagnosis. The present value of these methods would appear to be as follows:

(1) *Radiology:* Radiography is invaluable in arousing the first suspicion and it is unusual not to be able to demonstrate, at least indirectly, a carcinoma of the lung that is producing symptoms (Liebow, 1952). However, the findings are very often inconclusive. The figures given by Overholt and Schmidt (1949) show that there is usually a time lag of approximately 4·6 months in the average patient between the X-ray examination and the final diagnosis. The same authors also point out that the average patient consults a physician approximately 3·8 months after the first initial symptom and another 1·6 months pass before the first X-ray is ordered. Thus in the average patient, 10 months have already elapsed before a final diagnosis of bronchogenic carcinoma is made.

(2) *Bronchoscopy:* Table 1 shows that more than half the cases of bronchogenic carcinoma arise in the upper lobes of the right or the left lung. This is an area which is visualised by the bronchoscope only to a very limited extent, nor can the tumours situated in the periphery of the other lobes be seen. Thus only about 35 per cent. of the lesions can be visualised. If a biopsy is obtained a morphologic diagnosis can be made. Figures given by Herbut and Clerf (1946), who reviewed 336 bronchoscopy-positive cases, show that only a relatively small number of biopsy positive cases were suitable for treatment. This is apparently due to the fact that bronchoscopy reveals the tumours closest to the carina. These are the ones in which a successful pneumonectomy is least likely.

(3) *Exploratory thoracotomy:* This is a major surgical procedure, and most surgeons usually undertake such a step only after some morphological evidence of the lesion is established. This too may result in considerable delay.

It will thus be apparent that X-ray, bronchoscopy and biopsy have not succeeded in bringing the average patient with bronchial carcinoma to surgery early enough for a reasonably successful interference. Farber and Tobias (1947) have estimated the average survival time of a patient with bronchogenic carcinoma as 10-14 months. The great need for a diagnostic method which would recognise the condition early enough for effective surgical treatment is thus apparent.

TABLE 1.—DISTRIBUTION OF BRONCHOGENIC CARCINOMA IN THE VARIOUS LOBES OF THE LUNGS

	RUL	*LUL*	*RLL*	*LLL*	*RML*	*Total*
Fischer (1931) ..	148	130	129	105	15	527
Simmons (1937)	169	179	119	112	70	649
Willis (1948) ..	9	9	8	6	3	35
Total	326	318	256	223	88	1211
	644					

RUL—right upper lobe; LUL—left upper lobe; RLL—right lower lobe; LLL—left lower lobe; RML—right middle lobe.

TABLE 2.—CYTOLOGY IN THE DIAGNOSIS OF BRONCHOGENIC CARCINOMA

Observer	*Total number of patients*	*No. of patients without cancer*	*No. of patients with cancer*	*Histologic confirmation of cancer*[1]	*Correct positive cytologic diagnosis*		*False positive*[2] *cytologic diagnosis*		*Remarks*[3]
					Number	*Percentage*	*Number*	*Percentage*	
Barret (1937) ..			110		68/110	61·8	2		Represents Dudgeon's figures until 1937 (sputum)
Bussi and Manzocchi (1953)			100		87/100	87	Not available		Sputum examination
Clerf and Herbut (1952)			540		476/540	88·3	Not available		Bronchial specimen
Dudgeon and Wrigley (1935)	58	20	38	17/38	26/38	68	1/20	5	6 preparations from each specimen (sputum)
Farber *et al.* (1951)	2066			241		55	6		3 specimens on an average
Gower (1943) ..	93	30	63	21/63	36/63	64	0	0	Sputum examination
Hengstmann (1953)	130	57	73		57/73	78	6/57	10·5	Aimed bronchoscopic aspiration under fluoroscopy
Hjelt (1953) ..			244	171/244	153/244	63		2·6 of all cases	Sputum examination
Hjelt (1953) ..			47	39/47	37/47	79		3·3 of all cases	Bronchial specimen
Iversen (1953) ..	873	629	124			46		1·4	
Jackson, Bertoli and Ackerman (1951)	270	170	100	81/100	61/100 and 8 suspicious	61	4/170	2·4	3 samples (sputum) 4 smears each. Modified Pap. technique

Jackson, Bertoli and Ackerman (1951)	270	170	100	81/100	61/100 and 8 suspicious	61	4/170	2·4	3 samples (sputum) 4 smears each. Modified Pap. technique
Jennings and Shaw (1953)	958	563	395	290/395	240/395	60·7	6/563	1·05	Sputum specimen. Wet film methylene blue stain
Kjaer, Dreyer and Hansen (1950)	273	125	123		46/123 and 30 suspicious	37	14/125 and 11 suspicious	11·2	Sputum examination
Kuesko and Portele (1949)	488		124/145 verified	124	93/124	75	3		Over 3 samples of sputum on an average
Liebow, Lindskog and Bloomer (1948)	131 { 108 73	59 43	49 30	33/49 21/30	21/49 9/30	42·8 30	3/58 2/43	5·1 4·7	Sputum. Bronchial specimen
Mathews (1948) ..			33		24/33	72·7	2		Sputum cell-blocks stained with Hematoxylin-Eosin
McKay *et al.* (1948)			54		40/54	74	3		170 bronchoscopy examination specimens
Perrin and Littlejohn (1950)	741	119	55		33/55	60	2/119	1·4	Sputum. Methylene blue and carbolfuchsin, or iodine solution stain
Wandall (1944) ..	250	66	100	83/100	84/100	84	6/66	9·1	Sputum smears fixed in Schaudinn's fluid
Watson *et al.* (1949)	400		236		139/236	60	Not available		
Woolner and McDonald (1950)	6000				400	70		2	

[1] By biopsy on bronchoscopy, lymph node biopsy, resected lung or at autopsy.
[2] Number of incorrect diagnoses as related to the negative cases, unless specified as applicable to the entire series.
[3] Unless specified the specimens included both bronchial and sputum preparations.

In recent years cytology has been added to the available methods for the diagnosis of bronchogenic carcinoma. The basic idea for the cytologic diagnosis of cancer is the fact that malignant neoplasms exfoliate from a free surface. Papanicolaou (1946) has compared this " to a curettage that nature keeps on performing continuously." Individual cells or clusters of cells shed constantly. Papanicolaou has very often emphasised that since clusters of cells also exfoliate, the available diagnostic criteria are not only cytologic but also histologic.

Cytologic studies for the detection of bronchial cancer are made either on bronchial aspirates or washings or on the sputum. Different methods have been employed for the fixation and staining of smears prepared from these smears. The technique used is of crucial importance to obtain the full value of the cytologic method and to eliminate disappointing results. The procedures are quite simple, but scrupulous care at each step is the *sine qua non* of a preparation suitable for a valid conclusion. The Papanicolaou technique (1942) has been used most often in the United States with good results. This method provides for adequate fixation of wet-films and employs a staining medium which enables examination of individual and clusters of cells to advantage: most of the Papanicolaou staining solutions are alcoholic. This enhances the transparency of the cells. A brief review of the salient points of the technique follows:

Collection of Material. (1) Sputum: As applied to the sputum a deep cough specimen is expectorated into a glass jar containing about 30 ml. of 70 per cent. ethyl alcohol for immediate fixation. The patient must be instructed to take a deep cough and should be told that salivary specimens are of no diagnostic value.

(2) Bronchial secretion: The method of obtaining bronchial secretions has been described in detail by Clerf and Herbut (1950). The secretions obtained at bronchoscopy are immediately fixed in 95% alcohol, the collection tube is rinsed two or three times with 95% alcohol and the washings are added to the specimen. If no secretion is available at bronchoscopy the bronchi are irrigated with normal saline and the washings fixed in the same way as the aspirate.

Preparation of Smears: Blood-tinged particles are especially looked for, and if absent, samples from different portions of the sputum picked up and spread evenly and thinly on at least three slides coated with Mayer's albumin. The smears are immediately immersed in the fixation fluid (equal parts of ether and 95% alcohol). Care is taken to avoid drying the smears.

The bronchial specimens are centrifuged for thirty minutes at medium speed. The supernate is decanted and a few drops of Mayer's albumin are added to the sediment. The smears are then made and fixed in the same manner as in the case of the sputum.

Staining: The slides are left in the ether-alcohol fixing medium for at least one hour before they are stained by the Papanicolaou technique (1942, 1943, 1954). It has been recommended that EA65, which contains half-strength Light Green, be used for staining bronchial and sputum smears rather than EA36, because the former gives a more transparent cytoplasmic stain. This is desirable for specimens containing much mucus.

The diagnostic successes and/or failures of different studies as reported in the literature are compiled in Table 2.

Discussion

Correct Positive Diagnoses:

It will be evident from the above reported figures that a correct positive diagnosis was made by the cytologic method in 37 to 88·3 per cent. of proved cases of lung carcinoma. Many authors stated that in the majority of cases a positive diagnosis was made on examination of the first specimen. However, multiple examinations increased the correct positive diagnoses considerably. Thus, in the experience of Farber and others (1949), when five sputum specimens were examined the accuracy of correct positive diagnoses rose to 90 per cent. (63 of 69 proved cases were reported positive). The number of slides prepared from each specimen would also seem to affect the results: this is evident from the rather low figures of Liebow (1948), who usually examined only one smear. Preparation of at least three smears from each specimen is recommended. Should there be doubt about the interpretation of available suspicious cells additional preparations should be examined. Adequately trained technicians are employed to screen the slides in a systematic manner, covering all the cells in each smear. Suspicious cells are marked with ink-dots. The final evaluation is made by a cytologist or a pathologist with proper training and adequate experience in cytology.

False Positive Results:

These have been obtained in 1·05 to 11·2 per cent. of the cases reported. A study by Iversen (1953) of 42 false positive cases reported by different authors showed that the misdiagnosed cells originated primarily in metaplastic foci seen in chronic inflammation. Woolner and McDonald (1947) had a false positive report in a case with extensive pulmonary infarction. In our experience, silicosis has been responsible for one false-positive report. In retrospect, many authors have felt that, by stricter adherence to cytologic criteria of malignancy, some of the false positive diagnoses could have been avoided (Jackson *et al.*, 1951). Farber and others (1951) and Clerf and Herbut (1952) have studied numerous samples and have been able to avoid false positives over a long period. The few false positive results they obtained were reported early in the studies, so that it seems that increased experience can largely eliminate false positive results. However, as emphasised by Jackson and associates (1951), it is important to recognise that these are one of the limitations of the cytologic method. It has been observed that following bronchoscopy false positive cells are liable to appear in the sputum (Jennings and Shaw, 1953; Farber and others, 1950). A sputum specimen should, therefore, be taken at least ten days after a bronchoscopic examination.

It need hardly be pointed out that the dependability of any diagnostic method must be gauged by the frequency of false-positive results. The number of false-positive results in the above table has been fairly low. In order to avoid such erroneous diagnoses, it is necessary that the examiner be well conversant with the normal range of cellular forms as well as the atypical but benign forms found in various pulmonary diseases. It is most important to have definite criteria of malignancy and to adhere to these in the interpretation

of smears. These criteria have been thoroughly described by Farber *et al.* (1950), Papanicolaou (1954), Wandall (1944) and Woolner and McDonald (1949). In order that the results be reliable the smears must always be finally evaluated by a pathologist with experience in cytology or by a well-trained cytologist. In the United States, pathologists have contributed in no small measure to the advances in different branches of cytology.

Bronchial versus Sputum Smears:

Clerf and Herbut (1952), McKay and others (1948) and Hengstmann (1953) have made their studies almost exclusively on smears prepared from aspirated bronchial secretions or bronchial washings. The percentage of correct positive results obtained in these studies is remarkably higher than those obtained by other workers who used sputum smears alone. In view of the large number of cases studied, Clerf and Herbut's figures (1952) are noteworthy. In cases of a positive cytologic diagnosis, bronchial studies have the definite advantage of localising the tumour in the absence of definite radiological findings. However, the difficulty of obtaining repeated specimens of bronchial aspirate is recognised. The relative ease in obtaining repeated samples of sputum, the relatively lesser cost to the patient, make the cytologic study of sputum a more practical diagnostic method. If positive results are obtained on sputum examination a bronchoscopy may follow and the exact location of the lesion may then be determined.

Cytology versus Bronchoscopy and Biopsy:

Table 3 shows the decided value of cytology *versus* bronchoscopy and biopsy alone in the diagnosis of bronchial carcinoma. In the different series there were approximately 30 per cent. of cases in which a positive cytologic diagnosis was obtained exclusively—*i.e.*, in which bronchoscopy and biopsy yielded negative results.

TABLE 3.—RELATIVE VALUE OF CYTOLOGY AS COMPARED WITH BRONCHOSCOPY AND BIOPSY

Observer	*No. of patients with cancer*	*Broncho-scopy and biopsy positive*	*Indirect broncho-scopic evidence*	*Cytology positive*		*Bronchoscopy completely negative, cytology positive*	
				Number	*Percentage*	*Number*	*Percentage*
Clerf and Herbut (1952)	540	167	180	476	88·3	156	28·8
Jackson *et al.* (1951)	100			61	61	18	18
McKay *et al.* (1948)	54			40	74	14	26
Jennings and Shaw (1953)	395	158		240	60·7	137	35

Cytology and Peripheral Tumours:

The difficulty in diagnosing peripheral lung tumours is well known. The excellent results of cytologic studies in the diagnosis of these tumours is shown in Table 4.

TABLE 4.—CYTOLOGY AND PERIPHERAL LUNG TUMOURS

Observer	*Number of peripheral tumours*	*Positive cytology*		*Positive bronchoscopy*
		Number	*Percentage*	
Farber *et al.* (1951)	60	36	60	None out of 45 done
Jennings and Shaw (1953)	42	27	64·3	Not given

TABLE 5.—CYTOLOGY AND RESECTABLE CASES OF BRONCHOGENIC CARCINOMA

Observer	*Total No. of resected cases*	*Visual evidence*	*Positive biopsy*	*Positive cytology*	*Positive cytology exclusively*	
					Number	*Percentage*
Clerf, Herbut and Nealon (1951)	137	67 (48·9%)	38 (27·7%)	68 (49·6%)	Not given	
Jackson, Bertoli and Ackerman (1951)	25	15 (60%)	9 (36%)	16 (64%)	4	16
Jennings and Shaw (1953)	161	Not given	57 (35·4%)	101 (62·7%)	64	39·8
Woolner and McDonald* (1950)	77	Not given	45	32	32	41·6

* Of the 77 resections 45 were carried out on the basis of the biopsy and 32 on the smear report alone.

Operable Bronchogenic Carcinoma:

Cytologic diagnosis has appreciably increased the percentage of operable cases of bronchogenic carcinoma (Table 5). In many instances cytology provided the only pre-operative morphologic evidence of the lesion.

Metastatic Lung Tumours:

In the case of metastatic lung tumours cytology has not been of much help. Ellis and others (1950) achieved an accuracy of only 11·8 per cent. in a series of 34 metastatic lung tumours. The explanation offered is that the metastatic growth seldom crosses the barrier of the bronchus and thus no exfoliated tumour cells are available.

Summary and Conclusions:

Cytology has increased the diagnosis of all cases of bronchogenic carcinoma by approximately 30 per cent. (Table 3). As seen in Table 5 the number of resectable cases has been increased by means of the cytologic diagnosis in the order of 16-41·6 per cent. It is still too early fully to evaluate how much the cytologic method will assist victims of pulmonary cancer. This must await a more widespread use of the method as well as an adequate time lapse. However, an indirect approach to this point—that of operability rate in a particular series of cases—affords a clue. In this respect Clerf and Herbut's (1950) figure of 41 per cent. is noteworthy and is close to that of Ochsner's 35·8 per cent. (1952).

Clearly the present bleak outlook in bronchial carcinoma would be vastly improved if some way could be devised to see the patient and recognize the process early. A routine cytologic screening of the sputum of all men above the age of forty is probably not a practical proposition. The suggestion offered by Overholt (1950) that lung cancer detection be combined with radiological surveys for tuberculosis seems more practical. Thus, if in routine radiological surveys for tuberculosis a pulmonary lesion is noted in an elderly person, appropriate studies of the sputum for tuberculosis and/or cancer could be carried out as a routine.

It is gratifying that positive cytological findings have been obtained very early. At least one case of carcinoma-in-situ of the bronchus has been so diagnosed and reported in the literature by Papanicolaou and Koprowska (1951). There is now enough evidence that more widespread use of the cytologic method in the diagnosis of bronchogenic carcinoma will result in bringing the patient to surgery early enough for more effective treatment than has been possible in the past. It is, however, also true that cytology does not replace but supplements the other available diagnostic methods.

I am indebted to my teacher and chief, Dr. Ephraim Woll, M.D., Associate Professor of Pathology and Director of Laboratories, Mary Fletcher Hospital, whose effective instruction and guidance have made this paper possible.

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CARCINOMA OF LUNG APPEARING DURING TREATMENT OF PULMONARY TUBERCULOSIS

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An increasing number of cases are being reported of co-existing pulmonary tuberculosis and carcinoma of the lung (Fried, 1935; Gerstl *et al.*, 1946; Couts, 1951; Helm and Moon, 1952; Ellman, 1953). Such cases are seldom observed *ab initio*, for which reason the following case is of interest, and an attempt is made in retrospect to discover why suspicion was not aroused at an earlier stage.

History. D.F., aged 65 years: metal cannister-maker. Pulmonary tuberculosis was discovered by routine Mass Miniature Radiography of his factory group in December 1953, when his miniature film showed abnormality in the left lung. A large film was taken and he attended the Chest Clinic, Dunedin Hospital, when he was seen by Dr. R. F. Wilson, Senior Chest Physician.

Past History. 1950: Pneumonia, left lung; four weeks in Dunedin Hospital. 1952: Sciatica; four weeks off work at home.

No other illnesses: no family or other contact with tuberculosis known. On interrogation he admitted to having had a dry cough occasionally over the past five years, with increase of cough and a trace of mucoid sputum for the past four weeks: no loss of weight or energy. Appetite and sleep good. Slight dyspnœa on exertion. *Tobacco*: 4 oz. per week in the form of cigarettes rolled by himself. *Alcohol*: Occasional glass of beer or whisky. No history of V.D.

On examination. The patient was a thin, wiry, cheerful man, looking younger than his age. No glands were palpable. Physical signs in the chest were confined to diminished movement and expansion of left upper chest, where a few post-tussive crepitations were audible and whispering pectoriloquy was noted. Other systems appeared normal.

Weight 120 lb. *Blood Pressure* 90/50. *E.S.R.* 72 mm. in one hour. Owing to lack of sputum a laryngeal swab was taken and this produced a *Positive* culture for tubercle bacilli late in February 1954.

X-ray film dated December 10, 1953, showed " calcified lesions scattered throughout the left lung with fibrotic changes and pulmonary collapse in left upper lobe with probable activity. Right lung clear." (Plate 1.)

In view of the positive laryngeal swab culture, he was admitted to Wakari Chest Hospital on March 1, 1954.

On examination there was no change in the physical signs, but his weight had increased by 9lb. to 9 st. 3 lb. and E.S.R. had dropped to 18 mm. in one hour. He had a trace of mucoid sputum, which showed tubercle bacilli on direct smear and culture, on March 3, 1954. He was treated with five weeks' bed rest, together with streptomycin 1 G. daily for six weeks and thereafter 1 G. every third day, together with P.A.S. 12 G. daily. (Sensitivity tests showed high resistance to I.N.A.H.)

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In view of his good general condition he was rapidly upgraded and discharged in June, to continue streptomycin 1 G. twice weekly with P.A.S. 12 G. daily, and attend the Chest Clinic; by this time his sputum had converted to negative cultures. *Weight* 9st. 12 lb. *E.S.R.* 8 mm. in one hour.

Progress is shown below by relevant extracts from clinic notes.

July 8. Condition good. Rhonchi in left upper zone. No adventitia. Laryngeal swab negative on culture. E.S.R. 12 mm. in one hour. *X-ray film:* Fibrosis and calcification in left lung. In the right lung a round shadow 1·5 cm. by 1 cm. had appeared under the first rib. (Plate 2.)

September 30. Reported an attack of " flu " one week previously: aching limbs and irritable tracheal cough with sputum up to ½ oz. daily and twice stained with blood. *Chest:* No adventitia. Weight 9 st. 13 lb. Laryngeal swab negative culture and streptomycin and P.A.S. stopped accordingly.

October 14, 1954. Feeling fit: Cough and sputum much decreased. *Chest:* No adventitia. *X-ray film:* Some increase in size of round focus in right lung (2·5 by 2·5 cm.). Left lung—no change. Weight 9 st. 10 lb. E.S.R. 10 mm. Laryngeal swab, negative culture.

November 22, 1954. Feeling fit: very little cough and a little white frothy sputum. No wheezing. No fatigue on walking two miles. *Film:* Round focus now measures 2·7 by 3·8 cm.) (Plate 3). Weight 9 st. 4 lb. E.S.R. 10 mm. Laryngeal swab, negative culture.

December 30, 1954. Cough troublesome on going to bed and occasional yellow sputum. Weight 9 st. 1 lb. E.S.R. 22 mm. Sputum, negative culture.

January 20, 1955. Reported that six days previously he had coughed up bloody sputum, dark in colour: no free blood. Sputum remained stained for four days, was thick and mucoid in character but showed no blood at examination. No fresh physical signs in chest. No palpable glands. *Film.* Round focus in right lung has greatly enlarged since November 1954 film (4·5 by 4·75 cm.). Left lung—no change. ?Tuberculosis, ?neoplastic, ?hydatid. *Weight* 9 st. 2 lb. *E.S.R.* 38 mm. Sputum, negative culture: laryngeal swab negative culture.

February 1, 1955. Admitted to Wakari Hospital. He reported slightly bloodstained sputum once during the previous week. His general condition remained fair: no palpable glands: no adventitia in chest. *Pre-operative film:* Further increase in round shadow (5 by 5 cm.). (Plate 4.) *Weight* 9 st. 2 lb. *E.S.R.* 46 mm.

February 10, 1955. *Bronchoscopy:* (John Borrie). Larynx: trachea, carina and left and right major bronchial trees normal. The right upper lobe bronchus showed no neoplasm, but deformity of the secondary carinæ.

Wassermann and Kahn tests—negative.

Casoni test—negative.

February 22, 1955. Segmental resection of posterior segment of right upper lobe (under general anæsthetic).

There was a slowly increasing lesion in the right upper lobe which required exploration. In view of his age neoplasm was likely. Hydatid investigations had been negative.

The right chest was opened through the bed of the right sixth rib.

The pleura was found firmly adherent to the parieties. Adhesions over the upper lobe were divided and the lesion was freed from its dense parietal attachment. The lesion was rounded and firm and occupied the posterior segment of the upper lobe. There was no hilar lymph node enlargement. In view of the previous tuberculous history, the possibility of a tuberculoma was again

considered, and, in view of his age and emphysema and the lack of any hilar lymph node enlargement, segmental lobectomy was decided upon.

Subsequent histological examination showed that the mass was a squamous-cell carcinoma, but no tumour deposits were revealed in the lymph node draining the affected segment. (Plates 5 and 6.)

The post-operative course was uneventful and he was admitted again to Dunedin Hospital on March 14, 1955, for deep X-ray therapy.

Discussion

On careful re-scrutiny of all the films it has been possible to detect a minute round focus, less than 0·5 cm. in diameter, peeping from under the lower border of the first right rib in a film taken in May 1954. This was not perceived at the time and it was not until July 1954 that a round focus was noted. (Plate 2). From recollection it was considered that probably a fresh tuberculous focus might be forming, and the main attention was directed on the culture results of sputum tests.

One month later the film showed no change and no suspicion was aroused. The October and November films showed some increase in the size of the focus, but in view of lack of symptoms (apart from the episode of bloodstained sputum during influenza in September), and physical signs, concentration was still focused on the state of the sputum, which continued to return negative cultures for tubercle bacilli.

It was not until the end of December 1954 that a rise in the E.S.R. suggested that all was not well, and it was realised that there had been a steady loss of weight since leaving the Chest Hospital in June.

No film was taken until January 20, 1955, when it was noted that the focus had greatly enlarged and that the E.S.R. had risen still higher to 38 mm. in one hour. Events moved faster after this and exploration was decided upon, with the results already mentioned.

Looking back, these faults can be detected:

(1) Too much attention was directed to the state of the left lung, both clinically and radiologically, and to sputum results.
(2) The slow but steady decline in weight did not attract sufficient attention.
(3) The possibility of dual pathology in a man of 65 was not considered in the earlier months.

The moral would appear to be that a round shadow, appearing in a clear lung and steadily enlarging, even with proven active tuberculosis in the other lung, should be viewed with very grave suspicion, especially in the older age group of male patients: a group which is steadily increasing in numbers in New Zealand and elsewhere.

Finally, it is of interest to record that the sputum on March 8, 1955, had reverted to *positive* for tubercle bacilli on examination of concentrated sputum, but remained negative on culture.

Summary

An emphysematous male aged 65 years developed a round shadow in the right upper lobe, which was seen to grow from small beginnings, while under

PLATE XXI

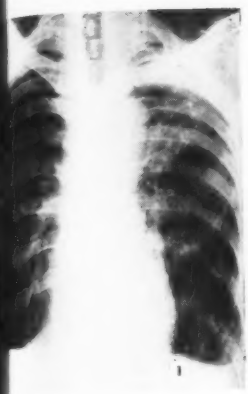


PLATE 1.—Pulmonary tuberculosis, probably active. Left upper lobe.

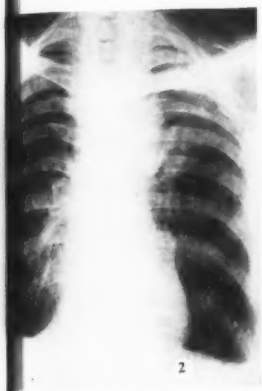
PLATE 2.—Round shadow first noted in right upper lobe under 1st rib. (1·5 by 1 cm.)

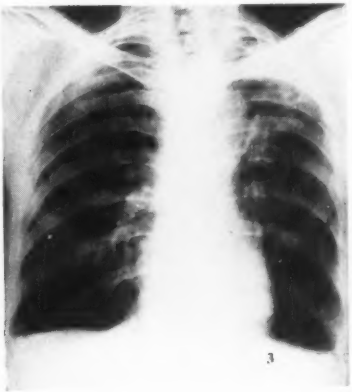
PLATE 3.—Increase in size of shadow, showing developed lesion. (2·7 by 3·8 cm.)

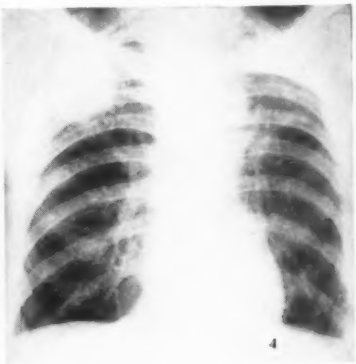
PLATE 4.—Pre-operative film. Shadow now 5 by 5 cm.

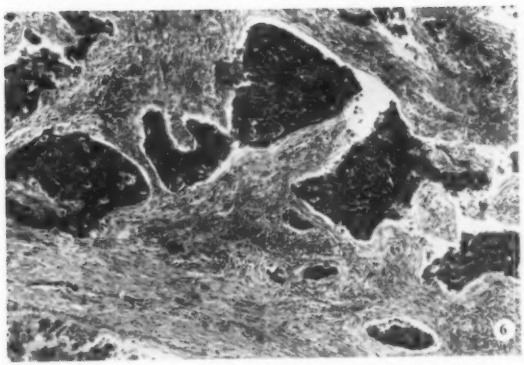
PLATE 5.—Microscopic appearances of resected mass.

PLATE 6.—Microscopic field showing squamous carcinomatous tissue.









To face p. 278

treatment for pulmonary tuberculosis of his left upper lobe. A squamous-cell carcinoma was ultimately resected. It is concluded that when a round shadow appears in a clear lung and steadily enlarges even with proven active tuberculosis in the other lung, it should be viewed with gravest suspicion, and early thoracotomy is advised.

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RESULTS OF RESECTION FOR BRONCHIECTASIS

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The first resection for bronchiectasis in England was done by H. Morriston Davies in 1913 on a man who subsequently served in Kitchener's Army. Excision did not, however, become an accepted form of treatment for another twenty-five years, but sufficient time has now elapsed for an assessment of results to be made.

The purpose of this paper is to record the results of such surgery in a consecutive series of cases, all of whom have been followed up for at least two years. The period chosen began in the summer of 1945, when an official Thoracic Surgery Unit was opened, and comprises 245 cases and 273 resections. Slightly less than a quarter of the patients seen in this period were advised to have surgery, though the percentage would undoubtedly be less for an unselected group of cases of primary bronchiectasis as proved by bronchogram.

The following tables are self-explanatory with the notes attached to them. Under other features information drawn from a study of cases operated upon by me since 1938 has been used, but all statistics presented relate to the above series.

Table I. General Statistics

	Type of Operation	
Cases: 245—Male 127; female 118.	Pneumonectomy	38
Age: 1 yr. 11 mths. to 63 years.	Unilateral subtotal resections	203
	Bilateral resections	24
	Resection in diffuse disease	8
	Pathology	
Resections: 273—Male 143; female 130.	Cylindrical 2/3. Saccular 1/3.	
Time: 14 mins. to 3 hours.	The latter mainly in upper lobes almost always in post-operative recurrence, probably always in congenital cases and incomplete resolution of staphylococcal infections.	
Sex distribution not significant at any age.	Marked collapse present 40 per cent. cases.	

Two points are worthy of note, firstly, the incidence of collapse (apneumatosis) is only 40 per cent. and it is not an etiological factor in the majority of cases; and secondly, the patient aged 63 was wrongly thought to have a cancer as well as bronchiectasis.

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TABLE II.—RESECTIONS

Age		*Area removed*			
1-10 .. 67	Rt. lung 7	Lt. lung 31
11-20 .. 81	R.U.L. 11	L.U.L. 14
21-30 .. 69	R.M.L. 19	Lingula 2
31-40 .. 39	R.L.L. 8	L.L.L. 91
41-50 .. 14	R.U.L. and R.M.L. 2	
51-60 .. 2	R.M.L. and R.L.L. .. 22	L.L.L. and L. 35
61-70 .. 1	Lobe and segments .. 7	Lobe and segments .. 35
	Segments 7	Segments.. 12
273=	83+	190

TABLE III.—IMMEDIATE MORTALITY (5 CASES—2%)

Unilateral Disease (2 cases)

Lobectomy, segmental resection—none.

Pneumonectomy, extrapleural—2; both shock, 2 and 6 hours after operation, in females aged 33 (right lung) and 49 (left lung).

Bilateral Disease (2 cases)

F. 32. R.M. and R.L. lobectomy (also disease L.L.L.), anoxia during operation.

M. 21. R.U. and R.M. lobectomy (14 weeks after L.L. lobectomy), anoxia 6 hours after operation.

Diffuse Disease (1 case)

M. 22. L.L. lobectomy—empyema—fistula—aspiration 12 days after operation.

("Immediate Mortality" includes any patient with an unhealed wound, or drainage made at the time of the resection.)

LATER MORTALITY (14 CASES—5·6%)

Unilateral Disease (10 cases)

A. Pneumonectomy (4 cases):

F. 30 (rt. lung), 7 years, bronchopneumonia.
F. 23 (lt. lung), 7 years, bronchopneumonia.
M. 46 (lt. lung), 4 years, cor pulmonale.
M. 53 (lt. lung), 3 years. bronchitis.

B. Lobectomy (6 cases):

F. 17 (L.L.L.), 18 months, bronchopneumonia.
M. 4 (R.M. and R.L.L.), 5 years, pulmonary tuberculosis.

Four cases not related to bronchiectasis—cerebral trauma, acute abdomen, cancer, and cancer with pulmonary tuberculosis.

Bilateral Disease (1 case)

F. 33. L.L. lobectomy 11.1.49. Empyema 50% expansion. Recurrence bronchiectasis L.U.L. 1950. L.U. lobectomy 19.9.50. Empyema fistula. Closure fistula 5.2.51. Death 19.2.51. Secondary hæmorrhage. Also R.L. lobe affected.

Diffuse Disease (3 cases)

2 cases. F., aged 25 and 28, died of hæmoptysis (5 years later) and multiple lung abscesses (7 months later) without any relief.

1 case. M. 28, died of cerebral abscesses (22 months later), but with marked relief for 21 months.

Total Mortality

	Immediate	*Later*	*Total*
Actual	5 (2%)	14 (5·6%)	19 (7·6%)
Corrected	5 (2%)	10 (4·0%)	15 (6·0%)

Correction due to omission of 4 cases in which death was not related to the original bronchiectasis.

TABLE IV.—RECURRENCE OF BRONCHIECTASIS

Unilateral Cases (18)

Deaths: 3 (16·6%), but one was from acute abdomen, so 2 (11·1%) corrected mortality.
Poor results: 6 (33%) 2 with phthisis, 2 with empyema and drainage, 1 with cor pulmonale, 1 with scoliosis; but last 4 all at light work.
Satisfactory results: 9 (50%), after further surgery.

Bilateral Cases (4)

Death: 1, I.S.Q.1; improved 2 after further surgery.
Total recurrence rate: 22 (8·8%) out of 245 cases. Nine of these 22 cases were 11 years old or under, that is 12·5% of that age group. Recurrence appears to take place within two years, unless due to an acute necrotising infection.

TABLE V.—PNEUMONECTOMY

Cases: 28. Male 17, female 21. Right 7, left 31. Age 1 year 11 months to 53 years.
Deaths: 6. Immediate 2, later 4. (See Table III.)
Poor results: 3. One with phthisis (F. 33), 1 with permanent empyema and cor pulmonale (M. 51), and 1 with recurrent infections of opposite lung (M. 4).
Good results: 29 (75%).

Comments: 1 immediate death—age 47.
2 later deaths—age 46 and 53 (at 51 and 55).
1 poor result but improved—age 51 now 58).

Late age group severely handicapped and downhill course.

TABLE VI.—BILATERAL CASES

Cases: 15.
Resections: 24.
Deaths: 3—immediate 2, later 1. (See Table III.)
Recurrence (see Table IV).
Improved: 1 (M. 12. L.L.L+L. 1946, R.L.L. 1947). Shop assistant, but not capable of vigorous exercise.

Good results: bilateral operations. 6 cases, 12 resections.
Improved: unilateral operations. Two cases, and after 6 years not considered necessary to remove R.M.L. and L.L.L. (Previous resections were L.L.L. and R.M.+R.L.L.)

TABLE VII.—DIFFUSE CASES

Cases: 8. Deaths 4—immediate 1, later 3. (See Table III.)
Marked improvement maintained in 3 cases: 7, 8, 9 years.
Relief severe hæmoptysis 1 case: 3 years.

TABLE VIII.—UNILATERAL SUBTOTAL RESECTIONS OF LUNG

Resections		*Immediate mortality*	*Later mortality (corrected)*	
Lobes	20	0	1	
Lobe	120	0	1	(See Table III)
L.L.L.+L. ..	31	0	0	
Lobe+segment ..	12	0	0	
Segments	20	0	0	
	203	0	2	

Recurrences: 18 cases with 9 satisfactory results. (See Table IV.)
Remaining Cases: 179 (203—6 deaths and 18 recurrences).

Marked nasal sinusitis 4
Persistent tracheo-bronchitis 12
Not satisfied 2
} All clinically improved (one has chronic nephritis).

Leaving 161 satisfactory results.

Satisfactory Results: 161+9 (satisfactory recurrence cases)=170=85%.

Note: Segmental resections gave good results and conservation of the superior segment of the lower lobe was uniformly successful though the latter resection was never done in children.

(M=Male. F=Female. No. following=Age at time of first resection.)

Other Features

Pregnancy. Several pneumonectomy cases have had children and there has been no difficulty during pregnancy and parturition. About half of the lobectomy cases suffer from being " chesty " in the last three months, but improve on delivery.

Subsequent respiratory infections. The impression has been formed that both pneumonia and pertussis tend to have a prolonged course after lobectomy. Furthermore, judging by a long follow-up of cases operated upon since 1938, about 5 per cent. later develop pulmonary tuberculosis. There is usually several years' interval. One case (a child) out of about 500 resections developed miliary tuberculosis on the fourteenth post-operative day.

Residual cough. If productive, this is due either to bronchiectasis, tracheobronchitis or granulations at suture line of the bronchial stump. When non-productive it is often due to smoking and habit.

Respiratory function after resection:

(*a*) Ventilatory insufficiency. When this occurs it appears to follow pleural thickening consequent upon pleural effusion.

(*b*) Parenchymatous insufficiency does not appear to occur if at least two normally functioning and major lobes are left intact.

(*c*) Circulatory insufficiency is unlikely,
I, provided two major functioning lobes are left intact,
II, unless the patient indulges in strenuous exercise, when a temporary pulmonary hypertension may occur.
The onset of cor pulmonale appears to be related chiefly to chronic sepsis in the bronchial tree.

Conclusion

Lobectomy and segmental resection in suitably selected unilateral cases gives a satisfactory result in 85 per cent. of cases, and there should be no operative mortality in this group. Pneumonectomy is associated with definite mortality and morbidity, but with a 75 per cent. satisfactory result. Surgery is of increasing value in bilateral cases and offers welcome relief in some cases of diffuse bronchiectasis.

THE DANGERS OF BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS

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The earliest attempts to outline the trachea, bronchi and alveoli by an opaque medium were made in America by C. A. Waters, S. Bayne-Jones and L. G. Rowntree in 1917. These observers used an oily emulsion of iodoform, in animals. The substance was so poisonous, however, that many of the animals died, and the method was never used for human beings.

In 1918 Chevalier Jackson insufflated bismuth powder through a bronchoscope. This was successful, but required skilful use of the bronchoscope, and was, therefore, never adopted for general use.

In 1921 Forestier and Leroux first succeeded in getting good pictures of the bronchial tree by means of Lipiodol, a compound of iodine and poppy-seed oil, containing 40 per cent. of iodine by weight.

Since this time Lipiodol has been used with great success to show the outline of the bronchial tree, and so established has this become that a term, " Lipiodol," has been coined for the procedure: in point of fact this is indefensible, as many other products are now used and a trade name is hardly a synonym for an everyday investigation which is probably best covered by the term " Bronchography."

Three to four hours after injection 70 per cent. of the oil will have been expectorated. The rest remains in the lung indefinitely and very little is absorbed. Archibald and Brown (1925) have recorded cases which show " plugging " of bronchioles and alveoli with oil with resulting collapse of lung and shortness of breath. This was not prolonged, but Jacoboeus, Selander and Westermark (1929) have reported cases of acute massive collapse.

The principal disadvantage of the retention of the Lipiodol in the lung is that it produces X-ray changes for many years afterwards which may be a serious nuisance and difficulty from a diagnostic point of view. Attempts have been made to overcome this by mixing Lipiodol with Sulphadiazine, and then nearly all the opaque medium is coughed up immediately afterwards. Dionosil, in both watery and oily solution, has also been used (Don, 1952; Adler and Faursinger, 1952); it is absorbed in the lung and is excreted by the kidneys. Cummins and Silver (1953) reported on 26 cases from Papworth. If a watery solution is used excretion is rapid but with an oily solution retention in the lungs persists for up to two months. Lung tissue was examined histologically in four cases at periods varying from a few days to seven weeks after bronchography. At first a large amount of oil was found free in the alveoli and alveolar walls but in tissue examined at seven weeks oil was seen as only an occasional globule, often within a phagocyte. It does not, however, give quite such a good definition as Lipiodol and is still an iodide preparation.

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Iodism may occur though it is not common and generally consists merely of lacrimation and hoarseness. Circinate localised erythema, laryngeal œdema, vomiting, diarrhœa and conjunctivitis may also occur. Febrile reaction and pulmonary infiltration has been described by Kooperstein and Bass (1946). Scadding (1934) reported a fatal case and this suggests the wisdom of testing the iodine sensitivity of the patient before using the oil. This can easily be done by giving the patient 10 grains of potassium iodide thrice daily for two days. Two fatal cases in which water-soluble media were used have been described by Peck, Neerken and Salzman (1953).

The older generation of physicians was aware that pulmonary tuberculosis tended to be activated by iodine and its derivatives and so was always careful to avoid giving it to patients with this disease. In recent years this opinion has tended to be disregarded and even denied and bronchography has, in some places, been carried out in patients with chronic pulmonary tuberculosis (Boyer, 1946; Ibers and others, 1951; Anacker, 1953), since it was considered in no way dangerous in chronic cases with cavities and it has proved valuable in defining the extent of these cavities. Marchese, Klassen and Curtis (1952) reviewed 49 cases and claimed that Lipiodol bronchography did not appear to have an unfavourable effect upon the disease in any of their patients. Since the advent of chemotherapy, making the excision of segments possible, it has thus become a valuable investigation. Shaw, Collins and Macnamara (1954) showed from 100 cases from the London Chest Hospital that bronchography demonstrated a degree of segmental localisation not obtainable by other means and that new information was obtained in 77 of their cases. This is well shown by the following case, where as a result of bronchography it was possible to cure the patient by removing only the apical segment of the right upper lobe.

Case 1. A woman, aged 45, had for four years had attacks of gnawing upper abdominal pain lasting several hours. These usually occurred each evening for about a week, every three to six months. The pain was accompanied by eructation and borborygmi. A barium meal showed a " hypertonic stomach " and a cholecystogram two gall stones. She had had a productive cough for years and had lost 3 stones in six years.

She was admitted to the London Hospital on 21.3.54, when on examination she was a thin, anxious woman. Her blood pressure was 110/70. She was tender under the right costal margin. On 23.3.54, Mr. E. C. B. Butler performed a cholecystectomy. The duodenum was normal but the gall bladder was chronically inflamed and contained many stones. The common bile duct appeared normal and was not explored. After the operation she developed a cough with purulent sputum and fever and was found to have a collapsed lower lobe of her left lung. The symptoms responded to bronchoscopy, postural drainage and antibiotics. The X-ray of her chest showed right apical tuberculosis (Fig. 1). Her sputum showed tubercle bacilli on smear and her B.S.R. was 12 mm. in one hour. Tomography showed fibrosis and calcification with cavitation at the right apex. Bronchograms showed bronchiectasis of the apical segment of the right upper lobe (Fig. 2). Chemotherapy was started with streptomycin 1 g. thrice weekly and Marsilid 100 mg. t.d.s., and on 9.6.54 resection of the apical segment of the right upper lobe was performed by Mr. Geoffrey Flavell.

The thorax was entered through the bed of the sixth rib, which was removed. The apical segment of the right upper lobe was found to be mainly affected,

although there were scattered areas of induration in the rest of the lobe. After the apical segment had been removed a cavity was found in the anterior segment. This was locally excised and the edges were sewn together with tantalum gauze between. The thorax was closed with two drains. The specimen removed showed that the pleural surface over the apex was thickened in milky-white patches with many fibrous tags and the cut surface showed many encapsulated caseous tuberculous areas. On 17.6.54 the streptomycin was discontinued because of papular erythema and P.A.S. 4 g. q.d.s. was started. On 21.6.54 the Marsilid was discontinued because of emotional instability, and I.N.A.H. 100 mg. t.d.s. was started. On 1.7.54 the patient commenced to get up and on 8.7.54 streptomycin was substituted for P.A.S. On 21.7.54 the chemotherapy was discontinued. The total streptomycin dosage was 43 g. On 17.9.54 she was discharged home and allowed to get up for six hours a day, this to be increased by one hour a week. She has since made an uninterrupted recovery.

The following cases offer substantial evidence in support of the theory that iodine activates pulmonary tuberculosis and suggest that it is dangerous to use bronchography as a method of diagnosis in that disease. They contrast strikingly with the findings of Shaw, Collins and Macnamara (1954), who claimed that among 100 patients 72 suffered no ill effects; 22 had a transient fever of less than 100° F. and 3 had a temperature of over 100° F., but in no case was there constitutional disturbance. Spread of the disease was observed in only one case in the series, this being one of the cases in which sulphadiazine in iodised oil was used—the other 97 having watery Dionosil.

In these cases it was used to attempt to differentiate between pulmonary tuberculosis and bronchiectasis presenting with hæmoptysis. In Case 2 both conditions were present but the patient's sputum, which had shown no tubercle bacilli before bronchography, even after repeated examination, always contained tubercle bacilli subsequently, suggesting that the tuberculous lesion in the upper lobe had been activated by the investigation. Case 3 was a man who came to hospital complaining of hæmoptyses for which the cause was not evident. He was investigated by bronchoscopy, and the culture from the suckings from the right upper lobe bronchus were shown to have grown tubercle bacilli after his discharge from hospital. Bronchography had shown no abnormality. All specimens of sputum examined subsequent to this investigation, however, showed tubercle bacilli on smear. Case 4 presented with hæmoptysis for which no adequate cause was established. The small tuberculous lesion in the left upper lobe was obscured by the clavicle and first rib. Bronchography was carried out to exclude the possibility of bronchiectasis. Following this investigation the patient's condition markedly deteriorated and a tuberculous bronchopneumonia developed. The lesion at the left apex progressed and developed a large cavity. Here, then, rapidly progressive tuberculosis developed in the patient after bronchography.

Case 2. A woman aged 21 had for fifteen months had a cough with greenish sputum and had had three attacks of feverishness and malaise. For six weeks she had had pain in the left chest which was worse on coughing and on deep breathing.

She was admitted to the London Hospital on 23.4.54. On examination

she was a healthy-looking girl. She had a few rhonchi at the left apex. A chest X-ray on 8.3.54 showed an opacity in the left upper zone. Her B.S.R. was 24 mm. in one hour. Her sputum was persistently negative for A.F.B. Tomograms showed a large irregular cavity in the 4-cm. section, and a bronchogram on 7.5.54 showed cylindrical bronchiectasis in the basal branches of the left lower lobe. In spite of the negative sputum this was considered tuberculous in origin.

On 8.5.54 her B.S.R. was 48 mm. in one hour and her sputum was positive on smear and culture. X-ray of her chest showed a homogeneous opacity extending from the left hilum to the apex. On 13.5.54 chemotherapy was started with streptomycin 1 g. and Marsilid 300 mg. thrice weekly. From 10.6.54 Marsilid was given daily. On 24.9.54 the chemotherapy was changed to streptomycin 1 g., Marsilid 300 mg. and P.A.S. 16 g. daily.

On 6.10.54, Mr. Rowlandson performed a thoracotomy. The thorax was entered through the bed of the fifth rib, which was resected. The lower lobe was found to be small and collapsed and there was tuberculous infiltration in the upper lobe, mainly in the posterior segment, but there were small areas of disease in other parts, except the lingula. As the lower lobe was being freed, a tuberculous cavity in the posterior segment of the upper lobe abutting on the fissure was opened and segmental resection was, therefore, performed. The raw surfaces were sutured over streptomycin powder. The removal of the lower lobe was then completed and the bronchial stump was covered with an intercostal muscle graft. On 11.10.54 she had bronchoscopic aspirations for collapse of the left upper lobe, and on 14.10.54 she had a further bronchoscopy for collapse. On 25.10.54 Mr. Rowlandson performed a left phrenic crush. The chemotherapy was changed on 27.10.54 to streptomycin 1 g. thrice weekly and Marsilid 300 mg. daily, and on 6.11.54 the total streptomycin was 97 g., the Marsilid 159 days and the P.A.S. 35 days.

On 6.11.54 the residual part of the left upper lobe was well aerated, filling the left hemithorax. Her E.S.R. was 18 mm. in one hour. Her sputum was negative. On 18.11.54 she was allowed to get up and on 23.12.54 the chemotherapy was discontinued, the total streptomycin being 117 g. and the Marsilid 207 days. She was discharged on 5.3.55 in good health.

Case 3. A man aged 27 who in May 1950 had a chest cold associated with a small hæmoptysis. A chest X-ray taken at that time showed no abnormality. In September 1950 he had a second larger hæmoptysis and was admitted on 22.9.50 to the London Hospital for investigation. A chest X-ray showed a slight increased shadowing at the right apex. His sputum was negative on smear. A bronchogram on 13.9.50 showed no abnormality. A culture from the right bronchial tree suckings from bronchoscopy on 20.9.50 grew tubercle bacilli after the patient was discharged. He was followed up in out-patients.

In July 1951 he had another hæmoptysis, his sputum culture grew tubercle bacilli, and in August 1951 his sputum was positive on direct smear and a chest X-ray showed slight extension of the right apical shadow. The patient rested in bed at home and his weight improved steadily.

He was admitted to the London Hospital on 28.1.52, when on examination he was apyrexial. There were no physical signs in his chest. His B.S.R. was 5 mm. in one hour. There were no tubercle bacilli seen in his sputum. A chest X-ray showed residual soft infiltration at the right apex and tomograms showed two small cavities seen at 6 cm. The patient was given an eighty-four-day course of streptomycin and P.A.S. and on the eighteenth day of this treatment

a right artificial pneumothorax was induced. There were some apical adhesions. On 10.3.52 a right thoracoscopy was performed by Mr. Sanderson. The pleura was healthy. Two postero-lateral sheets and one apical mediastinal sheet were divided. The lung was freed down to 1 inch above the hilum. His further progress was uneventful. The patient started to get up on 17.4.52 and by 16.5.52 he was up two hours daily and increasing this by one hour per week.

His final investigations showed his sputum culture to be negative and his E.S.R. to be 5 mm. in one hour. A chest X-ray showed a right artificial pneumothorax and residual shadowing at the right apex. He has remained well since.

Case 4. A man aged 38 had bronchopneumonia 22 years ago followed by four operations for right-sided empyema. Since that time he has had chronic bronchitis, a persistent cough with frothy sputum and increased dyspnœa on exertion. In October 1951 a bronchogram was carried out at the London Hospital and showed no bronchiectasis. At the beginning of February 1952 the patient complained of blood-stained sputum and one week later had a further hæmoptysis. The patient attended again in March, when an X-ray showed bilateral pulmonary tuberculosis and his sputum was positive (Figs. 1, 2, 3).

The patient was admitted to the London Hospital on 12.4.52 and on examination was pale and breathless at rest. He had a fever of 99°-100° during the first fortnight in hospital. In his chest there were the scars of the rib resection at the right base posteriorly. His lungs were emphysematous and there were scattered rhonchi and coarse crepitations. There was an impaired percussion note at the right apex and fine crepitations were heard at both apices. An X-ray of his chest showed some lipiodol remaining in both lung fields and there was widespread soft infiltration with cavitation in both upper and middle zones. Tomograms confirmed the presence of cavities on both sides. His sputum was positive for tubercle bacilli and his B.S.R. was 105 mm. in one hour (Fig. 4).

Isoniazid 150 mg. daily was started on 19.4.52 and the dose was increased to 300 mg. daily on 26.5.52. Streptomycin 1 g. twice weekly was added on 12.6.52 and the patient showed a satisfactory response to treatment, his temperature falling to within normal limits and his B.S.R. falling to 30 mm. in one hour on 3.6.52. Serial X-rays taken at this time showed diminution in the size of the cavities. His sputum, however, remained positive and a left artificial pneumothorax was induced on 21.7.52. An adhesion section was attempted by Mr. Sanderson on 25.8.52. Isoniazid and streptomycin were discontinued on 11.8.52, but in view of the persistent positive sputum streptomycin 1 g. daily with P.A.S. 16 g. daily were started on 5.9.52. On 19.9.52 the patient had a spontaneous pneumothorax superimposed upon the left artificial pneumothorax and this was relieved by the withdrawal of 800 ml. of air. On 22.9.52 he complained of generalised aching, headache and conjunctivitis with an erythematous rash over the legs. This was thought to be a drug reaction, and streptomycin and P.A.S. were discontinued on 23.9.52 with subsequent improvement in his symptoms. On 19.11.52 a further thoracoscopy was carried out by Mr. Geoffrey Flavell. His sputum continued to remain positive and on 28.11.52 a course of Marsilid 225 mg. daily with streptomycin 1 g. three times weekly was started. This was continued until 29.1.53 but did not produce any significant improvement, his sputum remaining positive and the E.S.R. elevated. The November culture was found to be resistant to the isoniazid drugs but sensitive to streptomycin. Tomograms repeated in January showed that the cavities on both sides were considerably smaller. On 17.4.53 a right artificial pneumothorax was attempted under the cover of streptomycin

and P.A.S., but high positive pressures were obtained with small quantities of air and this was abandoned. It was felt that no further active treatment was practicable and that, in view of his emphysema and poor respiratory reserve, surgery would not be advisable. He was allowed to return home on 11.5.53 and to get up for four hours daily.

At the time of his discharge an X-ray showed a left artificial pneumothorax with many adhesions and residual small cavities at both upper zones. His sputum was positive for A.F.B. on smear, and his B.S.R. was 10 mm. in one hour.

He was again admitted to hospital, and a left upper lobectomy was performed by Mr. Geoffrey Flavell.

In the other cases to be recorded here, the result was disastrous. One was a woman aged 37 who had a chronic tuberculous lesion at the left apex over which was much pleural thickening, the end result of artificial pneumothorax therapy. Her sputum always contained tubercle bacilli. Bronchography was carried out in order to establish whether the tuberculous disease was sufficiently limited for lobectomy to be performed, since her emphysema was so severe that it was thought she could not survive pneumonectomy. Unfortunately, following the investigation, she became acutely and seriously ill with a tuberculous bronchopneumonia. She responded partially to treatment with viomycin but died six months later. There was not a necropsy.

Case 5. A woman aged 37 who in 1947 had a persistent cough. Her sputum was found to be positive and she was admitted to hospital in August. A left artificial pneumothorax was induced and the adhesions were divided. In November 1948 she was discharged feeling well, but she developed an obliterative pleuritis with the formation of fluid. In February 1950 her cough returned with hæmoptysis and anorexia and in October 1950 she was again admitted to hospital and a right artificial pneumothorax was induced. Following this she remained in bed and in March 1951 she was given a course of streptomycin and P.A.S. for three months. In April 1952 she had a right spontaneous pneumothorax and the right artificial pneumothorax was abandoned. She was given I.N.A.H. 150 mgm. three times a day for three months. Since then she has been breathless on the slightest exertion with a cough productive of 3 oz. of purulent blood-stained sputum a day.

On 26.9.52 her B.S.R. was 35 mm. in one hour and her sputum was positive on smear and culture. A chest X-ray showed further slight spread in the right mid-zone and an increase in the left apical pleural effusion. Tomograms showed a little scattered infiltration in the right upper lobe and the apex of the lower lobe without cavitation. The appearances in the left lung suggested a loculated apical effusion with many cavities, overlying a collapsed upper lobe. On 1.10.52 chemotherapy was started with Marsilid 75 mg. three times a day and on 23.10.52 the Marsilid was increased to 100 mg. three times a day. On 23.12.52 the Marsilid was discontinued after seventy-nine days. Mr. Rowlandson performed a bronchoscopy on 23.1.53 which showed the cords, trachea, carina and right bronchial tree to be normal and, in the left bronchial tree, the upper lobe orifice was normal but the first subdivisions were blocked by mucopus and were not aerating; the lower lobe bronchus was slightly narrowed but was otherwise normal. On 27.6.53 the chemotherapy was resumed with dimycin and P.A.S. and on 5.10.53 this was discontinued after 100 days.

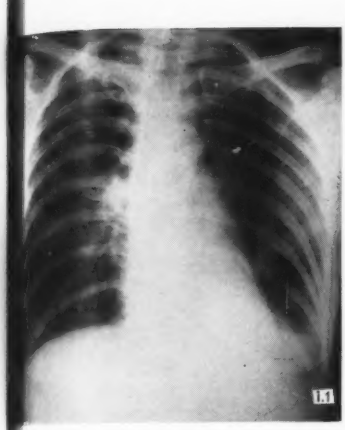
In March 1954 gradual extension of the disease in the right upper lobe began and in Mary 1954 persistent and increasing albuminuria was found. In July 1954 the bronchogenic spread was appearing in the right lower lobe and right apical tomograms showed several cavities in the right upper lobe. A left bronchogram with oily Dionosil was carried out and showed bronchiectasis of the upper lobe and apical segment of the lower lobe. The basal segments did not fill well because of retained secretion and some of the Dionosil entered the cavities in the empyema. The patient had had a slight irregular fever since April 1954, but after the bronchogram it gradually increased until four weeks later it was about 101°-102° each evening. An X-ray in August 1954 showed great increase in the scattered infiltration in the right lung (Figs. 1, 2, 3). A course of viomycin and P.A.S. controlled the toxæmia incompletely and in December 1954 albuminuria was abundant and the liver was palpable four fingers' breadth below the costal margin. It was then considered that she had amyloid disease. The patient became increasingly toxic and breathless and died on January 19, 1955. The sputum was constantly positive on smear and culture. On admission the organism was sensitive to streptomycin and resistant to I.N.A.H. and Marsilid. Resistance to streptomycin emerged in February 1954.

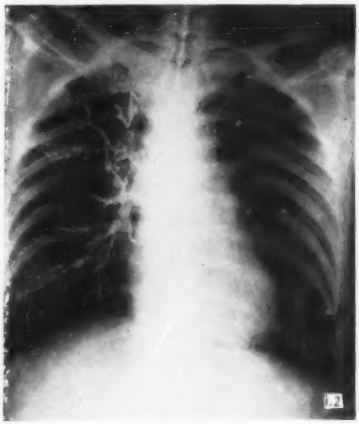
There was no necropsy.

Case 6 was a young woman aged 28 who had large cavities in both upper lobes which bilateral thoracoplasty had failed to close. Bronchography using oily Dionosil was therefore carried out in order to assess the extent of the disease so that excisional surgery might be considered. Within twenty-four hours of the investigation she became acutely ill with a high fever, anoxia and copious sputum. X-ray showed patchy mottling throughout both lungs. She died twenty days later. Necropsy showed that there was still oil present in the bronchi and that there was also a tuberculous bronchopneumonia.

Case 7. A woman aged 28 at a routine X-ray examination in July 1948 was found to have bilateral tuberculous infiltration and in October 1948 was admitted to Dagenham Sanatorium for six months. In June 1949 she had a baby in Oldchurch Hospital and she defaulted any further surveillance. In June 1950 her cough returned and in December 1950 an X-ray showed gross extension of the tuberculosis with bilateral apical cavitation. The patient remained in bed at home. In March 1951 she was admitted to Eastern Hospital and a course of streptomycin and P.A.S. was given to her and the cavities appeared to close. In January 1952 the patient was allowed up and the cavities "reopened." In April 1952 she returned to bed and a course of Rimifon was started, and in May 1952 she was transferred to Marillac Sanatorium, where Rimifon 300 mgm. daily was continued and streptomycin 1 g. twice weekly was added on 12.6.52. Serial X-rays showed progressive clearing, but her sputum remained positive and a right artificial pneumothorax was induced on 4.8.52. On 16.8.52 an X-ray showed a right artificial pneumothorax with thick apical adhesions holding out a large cavity. There was tuberculous infiltration at the left upper zone. Her sputum contained tubercle bacilli and her B.S.R. was 18 mm. in one hour. Rimifon with streptomycin twice weekly was continued until 4.9.52, when it was replaced by streptomycin 1 g. daily with P.A.S. 5 g. four times a day. A right thoracoscopy and adhesion section was performed by Mr. Sanderson on 25.8.52. This was followed on 2.9.52 by a febrile episode with pleuritic pain on the right side, but she had no

PLATE XXII

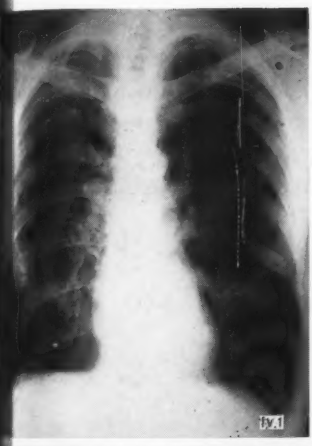


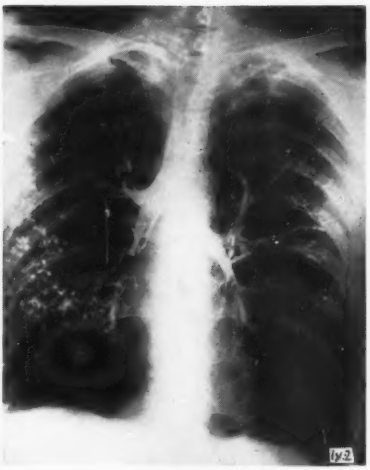


CASE 1

FIG. 1. — Woman aged 45 showing collapse of left lower lobe two days following cholecystectomy. She had sputum containing tubercle bacilli. Fibrosis in right upper lobe was noted.

FIG. 2.—Antero-posterior bronchogram showing bronchiectasis confined to right apical segment of upper lobe.





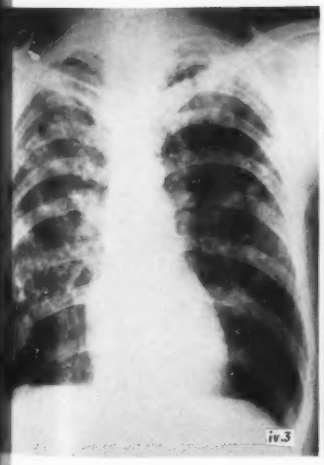
CASE 4

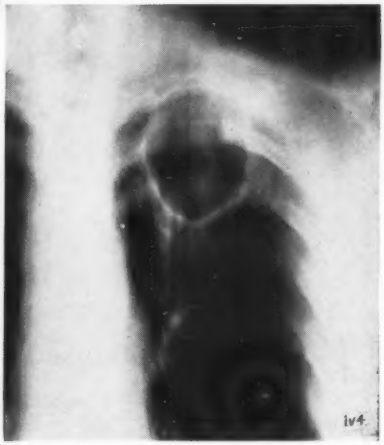
FIG. 1.—Man aged 38 complained of hæmoptysis. He had had a right-sided empyema twenty-eight years ago. There is a tiny area of infiltration behind the left clavicle.

FIG. 2. — Bronchogram of same patient

FIG. 3. — Tuberculous bronchopneumonia with cavitation at both apices developing within six months of bronchogram.

FIG. 4.—Tomogram showing the cavity at left apex.





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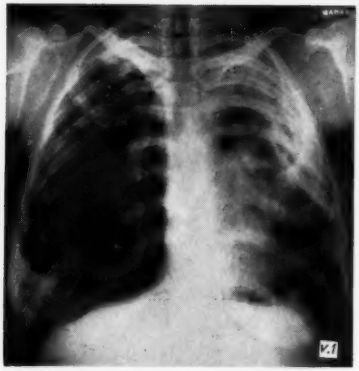
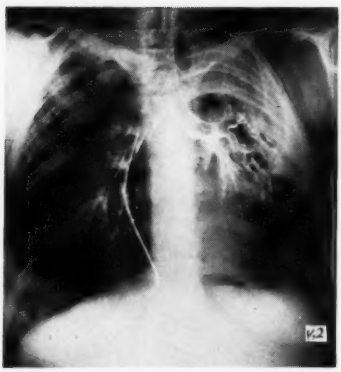
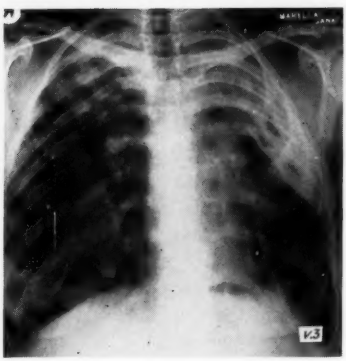




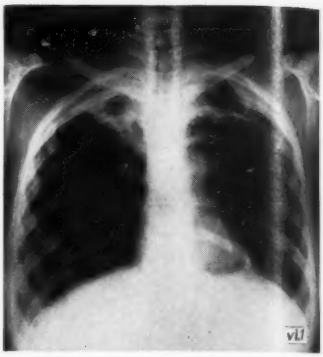


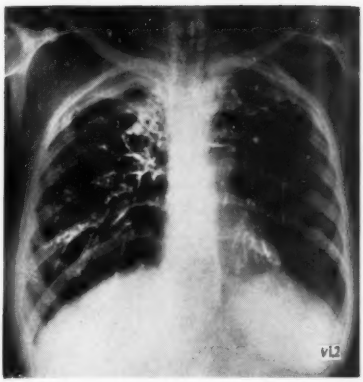
CASE 5

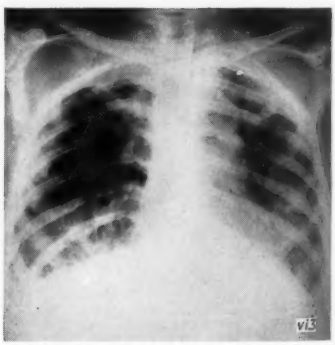
FIG. 1.—Woman aged 37. Tuberculous disease at both apices, more extensive at the left with cavitation.

FIG. 2.—Bronchogram to define the extent of the disease.

FIG. 3.—Following the bronchogram there was tuberculous bronchopneumonic spread. She died six and a half months later.







CASE 6

FIG. 1.—Woman aged 28 who had cavities in both upper lobes which had not been closed by bilateral thoracoplasties.

FIG. 2.—Bronchograms taken to show extent of disease prior to resection.

FIG. 3.—Tuberculous bronchopneumonia developing within 24 hours.

effusion. An X-ray after the operation showed a satisfactory collapse of the right lung, but the cavity was still visible in the collapsed upper lobe. This right artificial pneumothorax was abandoned in March 1953. A left artificial pneumothorax was induced in July 1953 and was abandoned in August 1953 because of indivisible adhesions.

In December 1953 both the upper lobes were contracted and contained large cavities. Lateral tomograms showed some infiltration in the apex of the left lower lobe without cavitation, but no infiltration in the apex of the right lower lobe. On 4.1.54 Mr. Vernon Thompson performed a first-stage left thoracoplasty and, following the operation, the patient became breathless and ill and it was decided to defer the second stage. The patient was discharged home to continue bed rest. She was readmitted on 7.5.54 complaining of hæmoptysis. Her B.S.R. was 33 mm. in one hour and her sputum was positive on smear and culture and resistant to streptomycin and I.N.A.H. On 5.7.54 Mr. Vernon Thompson performed a first-stage right thoracoplasty; the patient withstood the operation well and the right apical cavity was somewhat smaller. In order to assess the extent of the disease and to see if bilateral lobectomy was possible, a right bronchogram with oily Dionosil was carried out on 3.9.54 (Figs. 1, 2, 3). Within twenty-four hours the patient became ill with a high fever and copious sputum. The fever responded to aureomycin but the patient remained seriously ill with anoxia and copious sputum. Viomycin and P.A.S. were started on 15.9.54, as it was considered that the bronchopneumonia was tuberculous, but the patient quickly deteriorated and died of respiratory failure on 23.9.54.

Necropsy showed that the left lower lobe was converted into a cavity 4·5 cm. in diameter with white walls and surrounding fibrosis lying subpleurally and laterally and with no bronchial communication. There was some aerated lung tissue in the lingula. There were scattered yellowish-white chalky flecks around the cavity and in the lingula. The apical and lingular bronchi were clear. There was dense pleural fibrosis over the upper lobe and the lower lobe contained many hard yellowish-white granular nodules and many consolidated areas.

The right upper lobe was covered with equally dense pleural adhesions and contained a cavity 2·5 cm. in diameter with thick granular yellow walls. There were many hard nodules. There were grouped bronchogenic nodules throughout the middle and lower lobes mainly basally and subpleurally with no confluent areas. There was thick yellow mucopus in the trachea and main bronchi. There was a calcified tuberculous fleck in a right upper hilar lymph node.

The heart showed brown atrophy of the myocardium and moderate atheroma of the coronaries. The liver was congested. The spleen was twice its normal size. There were swollen congested kidneys, but otherwise the urogenital tract was normal.

Summary

Two cases are recorded in which patients developed tubercle bacilli in their sputum following bronchography with oily media. In a further three cases, tuberculous bronchopneumonia was precipitated by the investigation. This evidence supports the theory that iodine activates tuberculosis and shows, therefore, that bronchography is a dangerous investigation in patients suffering from that disease.

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ANKYLOSING SPONDYLITIS AND PULMONARY TUBERCULOSIS

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Introduction

Attention has been drawn before to the high incidence of pulmonary tuberculosis in ankylosing spondylitis. Fischer and Vontz (1932) found 3 cases of pulmonary tuberculosis in an analysis of 100 cases of ankylosing spondylitis. Fletcher (1951) found 8 cases of pulmonary tuberculosis in 90 consecutive cases of ankylosing spondylitis. Dunham and Kautz (1941) in a detailed analysis of 20 cases of this spinal disease found 25 per cent. to be suffering from pulmonary tuberculosis. They attribute this high incidence as compared with other figures to the allure possessed by the Desert Sanatorium, Tucson, for patients with tuberculosis: on the other hand, among 201 cases of rheumatoid arthritis admitted to the same institution, only 2½ per cent. had pulmonary tuberculosis. Hart *et al.* (1950) found 2 cases of active pulmonary tuberculosis in a series of 65 patients with ankylosing spondylitis. Ellman (1955) noted 8 cases of ankylosing spondylitis in a series of 300 cases of pulmonary tuberculosis.

The present enquiry began as an attempt to assess the incidence of ankylosing spondylitis in a group of sanatorium in-patients suffering from pulmonary tuberculosis. Attention was drawn to the problem by the accidental finding of a number of cases in the ward at the same time. As the enquiry developed, its scope widened to include problems of etiology, prognosis and treatment of the combined disorders.

Clinical material. All patients occupying beds in a 79-bed ward-unit for men in the State Sanatorium of West Australia during August-September 1954 were included in the study. Eighty-four cases out of a possible 87 were studied in detail, 3 patients in plaster casts being omitted. The average age of the group was 38 and the span 20-57 years. The unit under study took mainly acute cases in the under-55 age group, elderly and chronic cases being admitted to a different block. During the period under review, 192 males and 97 females were registered as in-patients of the sanatorium, which has 239 beds for the treatment of tuberculosis.

Diagnostic methods. All patients were questioned for a history of pains in the back or thorax. Examination was directed to find tenderness or limitation of movement in the thorax or any part of the spine. Where indicated, measurements were made of vital capacity and chest expansion at the nipple line. Where spondylitis was suspected, the spine was radiographed in the anteroposterior and lateral planes, and in some cases oblique views were taken.

In the absence of a satisfactory definition of ankylosing spondylitis based on

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etiology or morbid histology, the following descriptive definition adapted from Dunham and Kautz (1941) is accepted as a working standard. "Ankylosing spondylitis is a chronic progressive disease of the vertebral column and adjacent structures characterised clinically by pain and stiffness in the back. The small posterior intervertebral and the sacro-iliac joints are involved early in the disease and the costovertebral articulations are frequently affected. Ankylosis of involved joints tends to occur early. The bodies of the vertebræ undergo marked atrophy and the longitudinal ligaments of the spine may become calcified. The disease is subject to exacerbation and remission." For the purpose of diagnosis, ankylosing spondylitis is generally presumed to exist when a distinctive clinical disorder is accompanied by characteristic radiographic changes in the sacro-iliac joints. Dunham and Kautz (1941) regard these changes as non-specific. If their view is correct (and it would appear reasonable to require radiographic evidence of spondylitis to support a diagnosis thereof) the X-ray diagnostic criteria must include recognisable changes in more than one small posterior intervertebral joint. No case in the present study was included without characteristic sacro-iliac changes, though all had other evidence of spinal articular disease.

The diagnosis of pulmonary tuberculosis was based in all cases on the recovery of acid-fast bacilli from the sputum.

Case Descriptions

Case A is a mining engineer aged 39 who first noticed pains and stiffness in the spine in 1944. For several years he experienced severe pains in various parts of the thorax, memorable because he was terrified of coughing or sneezing. In 1951 he began to lose energy and weight. A chest X-ray showed exudative disease in the left upper lobe and the sputum contained acid-fast bacilli on direct smear. Earlier routine annual chest X-rays are available from 1942 to 1947 and show no evidence of tuberculosis. After preliminary chemotherapy, left upper lobectomy was carried out and was complicated by a broncho-pleural fistula and subsequent spread of his disease requiring pneumonectomy.

Examination shows an absolutely rigid dorsal and lumbar spine with some kyphotic deformity. Expansion of the chest is less than ½ inch. Screening shows respiration to be exclusively diaphragmatic. Radiography confirms the existence of bony ankylosis of the sacro-iliac joints and between the bodies of the lumbar and dorsal vertebræ. Many of the costovertebral joints show similar involvement.

Case B is a miner aged 43 who at the age of 27 began to suffer from lumbar backaches which continued intermittently for about three years. Annual chest radiographs taken of miners are available up to 1938, when his spinal symptoms were well established and show no evidence of tuberculosis. Routine X-ray of his chest in 1948, when he applied for work in this sanatorium, showed chronic fibro-caseous disease at both apices. Sputum smear showed acid-fast bacilli. In spite of the patient's earnest co-operation in treatment, which has included pneumoperitoneum and chemotherapy, slow progressive destruction of both upper lobes has continued, so that he is now fit only for sheltered employment.

Examination shows absolute spinal rigidity from the mid-cervical region to the sacro-iliac joints. In spite of a rigid thorax with an expansion of ¾ inch,

his vital capacity is 2,700 ml. Screening and X-ray in inspiration and expiration superimposed confirm the large diaphragmatic and small costal contribution to respiration. Radiographs show bony ankylosis of the sacro-iliac joints and between the bodies of the lumbar and dorsal vertebræ. There is bony ankylosis of many of the costovertebral joints and a lack of clear definition in others.

Case E, a 31-year-old labourer, first noticed fleeting pains about the shoulders and back ten years ago and has suffered on and off ever since. He was picked up on mass radiographic survey in early 1950 with bilateral fibrocavernous disease and a positive sputum. After 15 months' conservative treatment, 9 months of which were spent in sanatorium, he returned to full-time work with his lesions radiographically and bacteriologically healed. An X-ray taken before the commencement of radiotherapy during an exacerbation of backache in 1954 showed recurrence of cavitation in the left upper lobe. At the time of writing, the cavity is still unclosed and is awaiting resection.

This patient shows a moderate degree of rigidity of the dorsal spine. There is some symmetrical limitation of costal respiration. His chest expansion is $1\frac{3}{4}$ inches and his vital capacity 2,500 ml. Radiographs show bilateral sacroilitis and early ankylosis between the bodies of the lower dorsal vertebræ. The posterior intervertebral and lower costovertebral joints have a " woolly " appearance, indicative of early involvement.

Case G, aged 45, was picked up on radiographic survey of waterside workers in 1948. Bilateral chronic disease with cavitation was found and the sputum contained *Myco. tuberculosis* on direct smear. About May 1949, whilst undergoing conservative sanatorium treatment, he complained of lumbar backache and stiffness which has persisted more or less ever since. In 1950, apicolysis and plombage was carried out on the left side, with conversion of his sputum. He remained well until 1954, when he underwent a course of spinal deep X-ray therapy, and his next routine chest radiograph showed breakdown in the right upper lobe.

Examination of the spine shows a true poker back. There is considerable tenderness over the lumbar paravertebral muscles and the sacro-iliac joints. Costal respiration is markedly and asymmetrically diminished with a recorded chest expansion of 1 inch. The vital capacity is 2,900 ml. which is demonstrated by screening to be due to a good diaphragmatic movement. Radiography shows bony ankylosis of the sacro-iliac, lumbar and lower dorsal regions with earlier changes elsewhere in the spine. There is obliteration of the lumbar posterior intervertebral joints and evidence of ankylosis in the costovertebral joints.

Case L is a migrant labourer aged 38. Since 1951, when he "strained his back " at work, he has suffered from continuous backache, varying only in severity. He has complained of frequent and widespread pains about the thorax and of a heavy feeling in the sternum on inspiration. In 1953 he began to lose weight and energy. A chest X-ray was taken and showed bilateral diffuse infiltration and the sputum was found to contain tubercle bacilli. With rest and chemotherapy, his sputum has converted and serial X-rays show steady resolution of his disease.

There is absolute rigidity of the dorsal and lumbar spines. Tender points have been found about the thorax at various times, particularly in the costochondral regions and around the scapulæ. There is moderate symmetrical

limitation of costal movement with a chest expansion of 1½ inches. Screening demonstrates good diaphragmatic movement and double exposure of a chest film in inspiration-expiration confirms the poor costal component of respiration. Radiographs show gross spondylitis of the lumbar posterior intervertebral joints and advanced sacro-ilitis. There is early bridging between the bodies of D12-L1 and L4-L5.

Findings

Out of 192 adult males occupying beds during August-September 1954 in the State Sanatorium of West Australia for the treatment of tuberculosis, 5 were found to have ankylosing spondylitis. Of this total, only 84, comprising roughly the age group under 55, were studied in detail. The ward unit admitting the older males contained a higher proportion of stiff and painful spines but they were not included in the present report owing to difficulty in nosological analysis. It is widely accepted that ankylosing spondylitis is usually burned out by the age of 55 and the superimposition thereafter of degenerative spinal arthritis renders clinical and radiographic identification difficult. Saskin (1930) has drawn attention to the common occurrence of sacro-iliac ankylosis after the age of 50. In a random examination of the available X-rays in this elderly group, 4 cases of extensive spinal ankylosis were found. Strong probability exists that they represent the end-result of ankylosing spondylitis in early life.

Figures relating to the incidence of ankylosing spondylitis are often of little value, as when they are derived from the study of specially selected groups—*e.g.*, rheumatism clinic studies. Assessments of the incidence in the population as a whole are few. Schmorl (1932) found 8 cases in 10,000 routine necropsies carried out at Dresden. West (1949) analysed figures obtained from the radiotherapy clinic at Bristol, which he believed to drain all active cases of ankylosing spondylitis from a population of 420,000. Working on this basis, he computed the incidence in the population "at risk" (*i.e.*, 70 per cent. of the whole) to be 1 in 2,000. Assuming the overwhelming majority of cases to occur in the male sex, (Fischer and Vontz (1932) describe 100 cases, all males), this would give an incidence for men at risk of roughly 1 in 1,000, which compares with 1 in 40 among the male patients of this sanatorium.

Five patients in this group had some degree of spinal limitation and pain which was not attributable to ankylosing spondylitis. Two are thought to be the late result of intrathoracic suppuration and its attendant surgery. One stiff, kyphotic dorsal spine is regarded as due to adolescent osteochondritis dorsi. It has not been possible to allocate the remaining two patients with certainty to any etiological group. Both show radiographic evidence of inactive sacro-iliac arthritis. Both patients give a history of injury to the back and both, since contracting tuberculosis, have complained of widespread symmetrical joint pains in the distribution of a mild generalised rheumatoid arthritis. In both cases the backaches preceded the development of tuberculosis by many years.

Changes in the thorax. Two of the five cases in the present series had no appreciable costal respiratory movement and less than ¾ inch chest expansion. The remainder had moderate or marked impairment of costal movement with chest expansions ranging from 1 to 1¾ inches. Vital capacities varied from

1,300 ml. in the case with only one lung (which compares with 1,900 ml. in another patient of the same age three months after pneumonectomy) to 4,000 ml. Screening showed good diaphragmatic movement in all cases. Double exposure of the chest X-ray in both phases of respiration gave some indication of the degree of limitation of costal movement. One case showed rib tenderness.

Radiographic changes. Anteroposterior and lateral radiographs of the dorsal spine were taken to demonstrate the anatomy of thoracic fixity. Three cases show extensive spinal ankylosis with bony ankylosis of costovertebral joints. Of the remaining two cases, both show early bridging of the lower dorsal vertebral bodies and one case shows evidence of active involvement of several costovertebral joints.

Discussion

Several authors have drawn attention to the frequency of pain and rigidity in the thorax in ankylosing spondylitis. Hart *et al.* (1950), who made a special study of the thorax in this disease, regard diminution of costal respiration as a cardinal diagnostic sign. Among the symptoms referable to the chest, they mention tightness of the ribs, aching on forced inspiration and sharp pain on coughing and sneezing. One or more of these symptoms were present in the majority of their cases and in two of the present group. Comroe (1944) had previously drawn attention to the common occurrence of sharp pains occasioned by sudden movements.

Observations of intrathoracic disease complicating or terminating ankylosing spondylitis have been frequent. The only case of von Bechterew's (1899) to arrive at post mortem died of pneumonia. Dunham and Kautz (1941) found the following complications in a series of 20 cases: pulmonary tuberculosis was found four times, pneumonia twice, pericarditis twice, chronic bronchitis and spontaneous pneumothorax each in one case. Hart *et al.* (1950) in their analysis of 65 cases made special enquiry for a history of respiratory disease. They found two cases of active pulmonary tuberculosis, two bronchitics, two pleurisies, two pneumonias, one asthmatic, one chronic spontaneous pneumothorax and one case of unexplained hæmoptysis.

In four of the five cases of combined pathology in the present group, there is no doubt that ankylosing spondylitis preceded the development of pulmonary tuberculosis by from two to ten years. In the fifth case, pains in the back developed about six months after admission to hospital for treatment of phthisis. In this case there is a history to suggest that there may have been an episode of spondylitis in early adult life.

Comroe (1944) regards pulmonary tuberculosis as a serious complication of ankylosing spondylitis, and in support of his view points out that in almost every instance the tuberculosis is not discovered till a year or more after the development of spinal symptoms. This view is supported by Assman (1925), Dunham and Kautz (1941), and overwhelmingly by the work of Hart *et al.* (1950). Kienböck (1938) regards ankylosing spondylitis as an exudative synostosing form of joint tuberculosis. Scott (1942) believes that the etiology of ankylosing spondylitis will ultimately be proven tuberculous, and quotes the high incidence of calcified mesenteric glands in support of his belief.

Fletcher (1951) describes pulmonary tuberculosis as an antecedent or concomitant factor in causation of ankylosing spondylitis. He quotes the work of Robinson (1940), who found that the percentage of positive tuberculin reactors was 30 per cent. higher in a group of 45 cases of ankylosing spondylitis than in a comparable group of rheumatic controls.

It seems paradoxical that a disease which immobilises the thorax should be accompanied by an increased liability to phthisis, yet the evidence points that this is so. It would be logical to assume, if it is accepted that ankylosing spondylitis is predisposing to pulmonary tuberculosis—and the findings from the present series suggest this—that the prognosis in the combined cases is poor. Of the five cases, four are readmissions to the sanatorium. One broke down in spite of effective apicolysis and another after ten months' rest in bed and apparent control of his disease. In one case, it is possible that deep X-ray therapy may be implicated as a cause of relapse.

In managing cases of the combined pathology, the physician will find himself in a dilemma; for rest, which is the cornerstone of the treatment of phthisis, promotes deformity and ankylosis of the spine and thorax. All writers on ankylosing spondylitis are agreed on the need for active and passive exercises as a basis for treatment throughout the course of the disease. It has not been felt justifiable to follow a régime of exercises in any of the cases in the present series. When thoracic surgery is contemplated in the treatment of tuberculosis, it should be remembered that cases of ankylosing spondylitis already have a diminished vital capacity. Hart *et al.* (1950) drew attention to the increased anæsthetic risk of patients with ankylosing spondylitis who are virtually dependent on their diaphragms for respiration.

The need for further study of spinal and rib movement in chronic respiratory disease has become apparent.

Summary

Five cases of combined ankylosing spondylitis and pulmonary tuberculosis are described among 84 adult male sanatorium in-patients between 20 and 57 years of age. Attention is drawn to the thoracic changes which occur in ankylosing spondylitis and to the frequency of respiratory disease as a complication. There is evidence to suggest a less favourable prognosis as regards the tuberculosis. Mention is made of some problems of treatment.

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THE TUBERCULIN JELLY TEST WITHOUT THE USE OF FLOURPAPER

By C. P. Silver

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Tuberculin jelly, since it is painless to apply, is now much used in tuberculin testing in children. The inaccuracies which beset the flourpaper method of performing the test have recently been described (Caplin, Harrington, Silver and Grzybowski, 1954). It seemed worth investigating the merits of the test without the preliminary use of flourpaper, and this account deals solely with the plain test.

All percutaneous tests are based on the specific skin reaction to tuberculin first noted by Moro and Doganoff (1907). Moro (1908) applied this specific reaction to diagnosis when he introduced his test, using tuberculin ointment. Comparison with other tuberculin tests showed that the Moro test was a little less sensitive than the Pirquet test (Hamill, Carpenter and Cope, 1908), and therefore definitely less sensitive than the Mantoux; this was especially so in children over 12 years of age (Madsen and Holm, 1935). To increase its sensitivity more concentrated ointments were devised (Hamburger and Stradner, 1919; Price, 1948). More extensive modifications of Moro's method include covering the tuberculin ointment with adhesive plaster instead of rubbing it into the skin, and the replacement of the ointment base with a jelly. This latter, the tuberculin jelly test (Monrad, 1936; Hart, 1938; Jensen, 1938), differs only from Moro's test in that it is applied without inunction and the jelly is kept in contact with the skin with adhesive plaster. Clark (1951) from a wide experience considered it to approximate to the 1 : 1,000 Mantoux test. Dick (1950) found a jelly containing 60 per cent. O.T. the most effective, and superior to jellies made with P.P.D.

Subjects and Methods

To test the efficacy of the jelly test simultaneous plain jelly tests and Mantoux tests were carried out on subjects showing different degrees of tuberculin sensitivity. The children tested fell into three main groups:

(1) Cases of active tuberculosis undergoing treatment, most of whom showed a high tuberculin sensitivity.
(2) School children from East London, most of whom were tuberculin negative.
(3) Children who had previously received B.C.G. vaccination. While tuberculin positive, the majority showed only a moderate tuberculin sensitivity.

A small group of adults and another of children at a day nursery were also

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tested. Jelly tests alone were carried out on the latter. The features of the various groups of children tested are given in Table 1.

TABLE 1.—SUBJECTS

Category	*No.*	*Age in years*	*Mantoux State (100 T.U.)*		*Remarks*
			+	−	
Cases of active tuberculosis	92	5-15	92	0	Tuberculin sensitivity determined
Cases of active tuberculosis	112	4-16	112	0	—
School children	196	5-11	23	173	Tuberculin sensitivity determined
B.C.G. vaccinated children	200	0-16	200	0	Tuberculin sensitivity determined in 80 children
Children at a Day Nursery	56	0-4	—	—	Jelly tests only performed

In many cases the tuberculin sensitivity was determined by the use of graded Mantoux tests. Starting with a weak dilution (1 T.U.) in known cases of tuberculosis and the 10 T.U. test in all other subjects, the weakest dilution of tuberculin which would produce a positive reaction was estimated. A positive Mantoux test was taken as induration of at least 5 mm. diameter, with or without surrounding erythema. The results were read at 48 hours except in the B.C.G. vaccinated children; these were read at 72 hours.

The tuberculin jelly used throughout contained 60 per cent. O.T. After cleansing of the interscapular area with acetone the tuberculin jelly was applied in the form of a V, the arms of which were about 2 cm. in length. A horizontal bar of control jelly 2 cm. long was applied above this. Both were covered with the same piece of plaster which was removed after 48 hours. The tests were read at various times up to 96 hours after application.

THE SKIN LESIONS PRODUCED BY TUBERCULIN JELLY

A survey was made of the skin lesions produced by tuberculin jelly in 288 children aged 5 to 15. One hundred and seventy-three children were negative to the 100 T.U. test and 115 Mantoux positive. Sixty-four were positive to 1·0 T.U., 39 to 1 T.U., 7 to 10 T.U. and 5 to 100 T.U., so that the tuberculin sensitivity of the group was high. The lesions observed have already been reported (Caplin *et al.*, 1954).

The jelly lesions observed at 72 hours were analysed in 199 children who had been vaccinated with B.C.G. at least two months previously. These received a simultaneous 10 T.U. Mantoux test, followed by a 100 T.U. test where necessary. All were positive, at least to the latter. In 80 the level of tuberculin sensitivity was determined by graded Mantoux tests. Forty-seven children were positive to 1 T.U. (the weakest dilution used), 24 to 10 T.U. and 9 to 100 T.U. Although not a fully representative sample, tuberculin sensitivity was clearly lower than in the cases of active tuberculosis.

The lesions found in both groups are shown in Table 2.

In tuberculin-positive children erythema, œdema and vesiculation were the common forms of reaction, and were most marked at 96 hours. In a vigor-

TABLE 2.—DISTRIBUTION AND TYPE OF PLAIN JELLY LESION IN NATURALLY INFECTED, UNINFECTED AND B.C.G. VACCINATED CHILDREN

Reaction	*Naturally infected group: Mantoux positive* 115			*Uninfected group: Mantoux (100 T.U.) negative* 173			*B.C.G. vaccinated group* 199
	Hours			*Hours*			*Hours*
	48	72	96	48	72	96	72
	percentage			*percentage*			*percentage*
Erythema	63	69	72	1	—	—	47
Œdema	27	48	48	—	—	—	37
Staining	3	—	9	—	—	—	2
Vesicles	56	66	77	—	—	—	35
Vesicopapules ..	17	10	3	1	—	—	14
Papules	14	7	3	1	—	—	22
Pustules	1	3	1	—	—	—	1
Crusts	—	—	—	—	—	—	3

ous reaction these lesions formed a solid V-shaped mark; in a weaker reaction, a patchy marking at the site of jelly application. Sometimes no reaction occurred though the child was tuberculin positive.

In the B.C.G. vaccinated children the skin reaction was considerably less marked than in the tuberculin-positive children with high sensitivity due to natural infection and, for the most part, active tuberculosis. Papules and vesico-papules were more common, but erythema, œdema and vesiculation, characteristic of the more vigorous reaction, occurred less often.

In those who were tuberculin negative, if inspected at 72 or 96 hours, no skin reaction of any kind was observed. This absence of jelly reaction in negative reactors was confirmed on another occasion in a further 179 children who were negative to the Mantoux test (100 T.U.).

These results were obtained in children over 5 years. It seemed possible that in younger children with more sensitive skins some reaction might be observed even in tuberculin-negative children. Fifty-six children attending a day nursery, aged 4 months to 4 years, were tested with jelly, but without a parallel Mantoux test. Four reacted to the jelly; one subsequently proved to be a notified case of tuberculosis, one was a contact with a positive Mantoux reaction, and two had converted after B.C.G. vaccination. In the remaining children, none of whom was known to have any contact with tuberculosis, no skin reaction was observed.

DEFINITION OF NEGATIVE AND POSITIVE JELLY REACTIONS

Occasional reactions occurred at 48 hours even in tuberculin negative children, so that the test should be read at 72 or 96 hours. If no skin reaction was observed the test was considered negative. Occasionally it may be difficult to decide whether or not any skin reaction is present. In this investigation if the skin reaction was so slight as to lead to real doubt as to its existence the reaction was classed as negative. If any reaction was noted at 72 or 96 hours the reaction was classed as positive. In practice this means that œdema

associated with erythema, or skin elevations (vesicles, vesico-papules or papules), were present. Definite erythema as the only feature was not observed.

Accepting these standards for positive and negative results, the sensitivity of the jelly test has been assessed in various ways.

The Jelly Test in Cases of Active Tuberculosis

Two hundred and four children under treatment in hospital for active tuberculosis, and ranging in age from 4 to 16 years, were tested with the plain jelly. In 92 tuberculin sensitivity was determined by simultaneous Mantoux tests. Of these 60 were sensitive to 0·1 T.U., 31 to 1 T.U. and 1 to 10 T.U.

The results of jelly testing in active tuberculosis are given in Table 3, where they are compared with those after B.C.G. vaccination. In 20 children the jelly test proved negative at both 72 and 96 hours. Under the age of 10 the test was negative only once, but in children aged 10 or more it was negative on 19 occasions—*i.e.*, in about one-sixth of the children tested. In a series of 18 adults with active tuberculosis half of the jelly tests proved negative.

Table 3.—Jelly Tests in Cases of Active Tuberculosis and After B.C.G. Vaccination

Age	*Cases of active tuberculosis*			*B.C.G. vaccinated children*		
	Number Tested	*Jelly Negative at 72 hours*	*Jelly Negative at 96 hours*	*Number tested*	*Jelly Negative at 72 hours*	*Jelly Negative at 96 hours*
0-4 ..	1	0	0	63	14	10
5-9 ..	77	1	1	74	22	12
10-16 ..	126	19	19	63	30	27
0-16 ..	204	20	20	200	66	49

Results after B.C.G. Vaccination

Two hundred children were tested with simultaneous jelly and Mantoux tests (10 T.U.) at least two months after B.C.G. vaccination. The lower sensitivity shown by this group has been referred to already. The size of induration of the Mantoux tests (10 T.U.) is shown in the figure appearing on page 304.

The jelly tests were read at 72 hours, but if no reaction was observed and the test appeared negative the test was re-examined after a further 24 hours. In one instance the test was read at 96 hours and not at 72 hours, and in seven children the second examination, at 96 hours, could not be carried out.

It can be seen (Table 3) that even in young children under the age of 5 the jelly test proved negative in about one-sixth. The same proportion of negative results was observed in children aged 5 to 9, and was much higher than in those suffering from active tuberculosis, where only 1 out of 77 children tested was negative. In older children the proportion of negative results had increased to rather less than half.

The Sensitivity of the Jelly and Mantoux Tests Compared

The jelly and Mantoux results have been compared in all positive reactors in whom tuberculin sensitivity was determined by Mantoux tests with graded dilutions of O.T. The numbers, though small, illustrate the trends which are apparent and the difference age makes to the plain jelly result. They are shown in Table 4.

Table 4.—The Sensitivity of Mantoux and Jelly Tests Compared

Mantoux sensitivity	*Jelly results at 72 hours*					
	Under 10 years			*Over 10 years*		
	No.	*Jelly +*	*Jelly −*	*No.*	*Jelly +*	*Jelly −*
+ve 0·1 T.U. ..	30	30	0	34	30	4
+ve 1 T.U. ..	18	18	0	21	18	3
+ve 10 T.U. ..	15	10	5	15	6	9
+ve 100 T.U. ..	8	0	8	6	0	6

Mantoux sensitivity	*Jelly results at 96 hours*					
	Under 10 years			*Over 10 years*		
	No.	*Jelly +*	*Jelly −*	*No.*	*Jelly +*	*Jelly −*
+ve 0·1 T.U. ..	30	30	0	34	30	4
+ve 1 T.U. ..	18	18	0	21	19	2
+ve 10 T.U. ..	15	10	5	15	8	7
+ve 100 T.U. ..	8	2	6	6	0	6

Up to the age of 10 years sensitivity of the plain jelly test appears to lie between the 1 T.U. and the 10 T.U. Mantoux test. Rarely a child who is negative to the 10 T.U. test but positive to the 100 T.U. Mantoux reacts to jelly test. The parallelism of the two tests is approximate only. Above the age of 10 the parallelism is less striking, and even children who are sensitive to 0·1 T.U. may prove negative to the jelly test.

It has also been possible to compare the results of the plain jelly test with the diameter of induration of the Mantoux test (10 T.U.) in the 200 children who had received B.C.G. vaccination. The size of Mantoux induration has been plotted against the age of the child and shown in relation to the jelly test result in the figure. The seven negative tests which could not be re-examined at 96 hours have been marked as negative on one occasion only.

It is clear that in children under 10 years the jelly results are closely related to the size of Mantoux induration, but this relationship is largely lost above this age.

Factors Affecting the Reliability of the Test

Time of reading

Better results were achieved by reading the test at 96 hours compared with 72 hours, particularly if tuberculin sensitivity was low. In cases of active tuber-

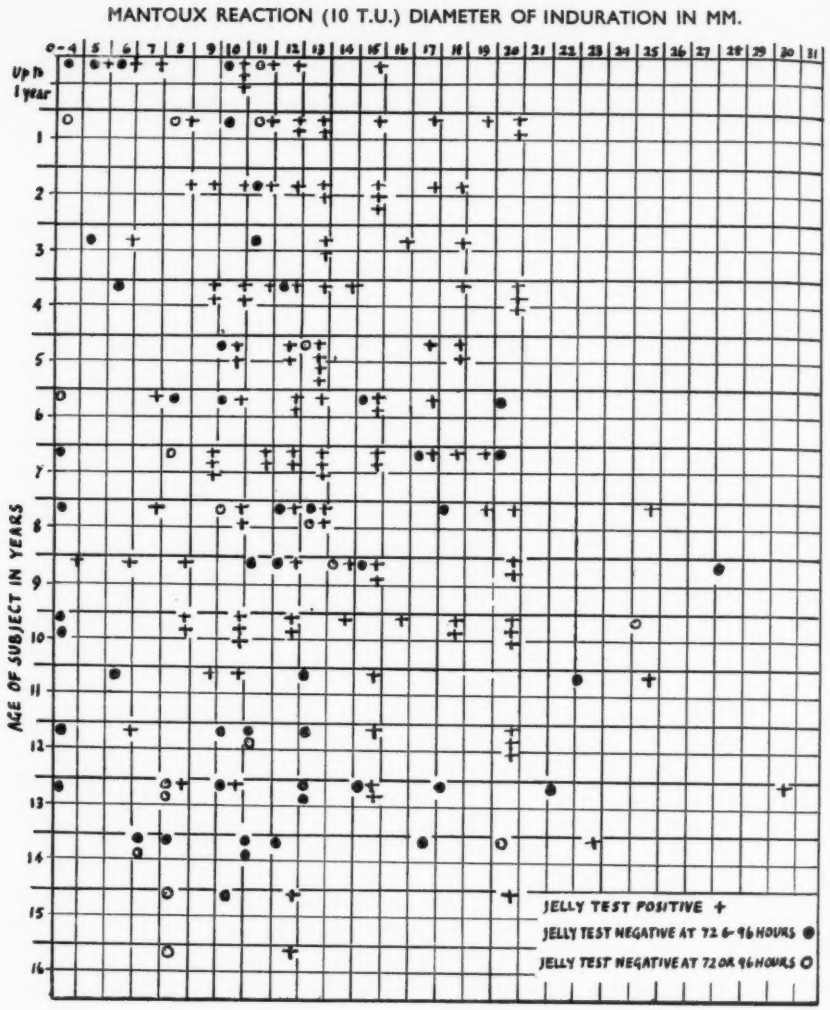

FIG. 1.—200 Children after B.C.G. vaccination. Jelly readings arranged according to the size of the Mantoux reaction (10 T.U.) and the age of the child.

culosis there was little difference, but in the 200 children tested after B.C.G. vaccination at least 11 out of a total of 66 negative results had become positive when read at 96 hours. Occasionally, however, a result judged positive at 72 hours may be negative at 96 hours.

Ease of reading

It was thought that different observers would find no great difficulty in reading the test, and that there would be none of the difficulty which has already been recorded with the flourpaper test (Caplin *et al.*, 1954).

Two observers with limited experience of the test independently read the plain jelly test at 96 hours on 329 children aged 7 to 11. Twenty-five of these children proved to be positive to the Mantoux test (10 T.U.) and 304 negative. The results of the two observers are summarised in Table 5.

TABLE 5.—CORRELATION BETWEEN EACH JELLY OBSERVER AND THE MANTOUX STATE (10 T.U.)

Mantoux state (10 *T.U.*)	*Readings of jelly observer Dr. P.*			*Readings of jelly observer Dr. Q.*		
	+ve	−ve	*Doubtful*	+ve	−ve	*Doubtful*
25 positive children ..	19	4	2	20	4	1
304 negative children ..	2	301	1	1	292	11

The correlation that they secured between the jelly readings and actual Mantoux state (10 T.U.) was therefore good, and there was little tendency to record false positive results. One observer recorded two and the other one only. In these three cases a further Mantoux test with 100 T.U. proved negative.

These observers had little difficulty in deciding whether the jelly reaction was positive or negative. Their doubtful results have been arranged in the order in which the children were examined (this order being indiscriminate and unrelated to age).

TABLE 6.—DOUBTFUL RESULTS

Order of examination	*Dr. P.*	*Dr. Q.*
First half of school	3	12
Second half of school	0	0

Of the twelve doubtful results recorded by Dr. Q. nine were in the first two classes examined. Clearly experience helped.

A similar trial was arranged with health visitors as observers, and the results were much the same, a good correlation with the Mantoux test.

KEEPING QUALITIES OF THE JELLY

Ounsted and Smallpiece (1951) ascribed occasional negative results to stale jelly. No difference was observed when tests using fresh jelly and jelly that had been kept for two years at 4° C. were compared in 23 children. No batch of jelly used in this investigation failed to produce positive reactions on one or more occasions.

THE CONTROL JELLY

Control jelly was always used except in tests performed after B.C.G. vaccination. A reaction at the site of the control jelly was never observed, and its use appears unnecessary.

Discussion

A comparison has been made between the plain jelly test and the Mantoux. It must not be thought that the Mantoux has been accepted as infallible and incapable of variation. Experimental errors in performing and reading the test have been surveyed by Nissen Meyer, Hougen and Edwards (1951). Non-specific reactions are known to occur, while the definition of a positive result and the time at which the test is read are not invariable. Even so all recent work suggests that the Mantoux is the most sensitive and reliable test known. Small inconsistencies between jelly and Mantoux tests are of trivial importance and should be disregarded.

Jelly tests in children under 10 years clearly reflect tuberculin sensitivity. It follows therefore that cases of active tuberculosis where high tuberculin sensitivity is the rule (Opie, 1930; Blair and Galland, 1931), and particularly cases of primary tuberculosis (Grzybowski, 1951), are likely to show a positive jelly result. In cases of pleural effusion where sensitivity is somewhat lower, though a positive result with the 1 : 10,000 Mantoux test is to be expected (Grzybowski, 1951), the jelly test is also likely to be positive. On the other hand, low tuberculin sensitivity has frequently been recorded in miliary tuberculosis and tuberculous meningitis. Taylor, Smith and Vollum (1953) recorded 22 per cent. of cases of tuberculous meningitis as negative to 100 T.U., so that a higher proportion, even of young children, is certain to be negative to the jelly test, and its use in these cases is wholly undesirable. Tuberculin jelly in young children cannot be used alone with complete security in the diagnosis of tuberculosis, though as a screening test, allowing the immediate subsequent use of the Mantoux test (100 T.U.), it is valuable.

After B.C.G. vaccination tuberculin sensitivity is not as high as after natural infection (Aronson, Parr and Taylor, 1941; Törnell, 1947). In this series standard Danish B.C.G. vaccine supplied by the Ministry of Health was used, 0·075 mg. being injected no matter what the age of the child. The Mantoux tests were performed two months after vaccination in 76 cases and one or more years later in 124. In every case the child was tuberculin positive, but sensitivity was lower than after natural infection. In younger children about one-sixth of the plain jelly reactions proved negative. This is too high a proportion of negative results for convenience in testing after B.C.G. vaccination, though the painless character of the test partly offsets this. As a preliminary to B.C.G. the plain jelly lies in strength between the 10 T.U. and the 1 T.U. Mantoux test.

The value of tuberculin jelly where the main interest is epidemiological cannot be questioned. MacDougall, Mikhail and Tattersall (1953) have described its use in such a survey of entrants to an infant school. This is likely to prove a useful method of case finding, since a positive result may lead to the discovery of an infected adult in the child's immediate family circle. Everything in such a survey is to be gained by the use of a reasonably accurate and painless test which, after instruction, can be applied by the school nurse. Similar satisfactory uses of the jelly include the routine tuberculin testing of children attending infant welfare clinics, day nurseries or nursery schools, and of small children on admission to hospital where the object is the detection of

tuberculosis in the family circle, or the discovery of a positive reaction in a child in whom a diagnosis of tuberculosis would not ordinarily be entertained. Here it is unnecessary to follow a negative jelly test with an intradermal test.

Above the age of 10 years the tuberculin jelly test proved ineffective. Evidently the jelly test result then becomes dependent upon the quality of the skin instead of the level of tuberculin sensitivity. In these older children even active cases of tuberculosis, with a sensitivity of at least 0·1 T.U., may prove negative so that it is ineffective even as a screening test.

Summary

The skin lesions produced by tuberculin jelly are described. In tuberculin-negative children no reaction was observed. In tuberculin-positive children, erythema, œdema and vesiculation were the most common reactions, but any definite skin change could be taken to indicate a positive result. The test was best read at 96 hours. In 204 children with active tuberculosis only one test proved negative in children under the age of 10, but 19 were negative in children of that age or more. In 200 children who had received B.C.G. vaccination the number of negative jelly results was much higher, at least 49 being negative at 96 hours. These negative reactions are related to levels of tuberculin sensitivity and to age. In children under 10 years the jelly test appears to be a reasonable index of tuberculin sensitivity and to lie in sensitivity between the 10 T.U. and 1 T.U. Mantoux test, but in children of 10 or more the relationship is much less close, and even those showing high tuberculin sensitivity, and sensitive to 0·1 T.U., may prove negative to the jelly test.

The jelly test is easy to read, and the material keeps satisfactorily.

I wish to thank Dr. M. Caplin, who has given me much help, and Dr. F. J. Bentley for permission to use material collected at High Wood Hospital for Children, where the active cases of tuberculosis were tested. I also thank Dr. K. F. W. Hinson, Dr. C. Crow, Dr. S. Grzybowski, Miss E. Hewison and Sister B. E. Hill for their help.

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THE EFFECT OF STREPTOMYCIN, ISO-NICOTINIC ACID HYDRAZIDE (ISONIAZID) AND STREPTOMYCIN PLUS ISONIAZID IN OCULAR TUBERCULOSIS IN ANIMALS

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The effect of chemotherapeutic drugs on experimentally induced tuberculous disease of the eye in animals has been the subject of several recent studies. Streptomycin in contrast and in combination with other anti-tuberculous drugs—the sulphones (Woods and Wood, 1948; Macaskill and Weatherall, 1950), para-amino-salicylic acid (P.A.S.) (Bietti, 1950; Horne and Macaskill, 1951), terramycin (Lepri and Capalbi, 1952) and isoniazid (Goulding and Robson, 1952; Bunn and Robinson, 1954)—have all been evaluated under varying experimental conditions. Some investigators have induced a tuberculous lesion of the cornea, but in this, as in previous studies, we have considered it better to obtain a standard lesion in the iris, as it is in the uveal tract that clinical ocular tuberculous disease is most commonly found. Bunn and Drobeck (1951) in discussing the use of the rabbit eye in the study of tuberculosis have also emphasised the importance of testing drugs in a form of disease which closely approximates human lesions. Furthermore, the effect of therapeutic drugs can very readily be observed in lesions in the anterior segment of the eye, small differences being readily recorded, under magnification if necessary, from day to day.

This report records some observations on the effect of streptomycin, isoniazid and streptomycin plus isoniazid on experimentally induced tuberculous disease of the iris in rabbits. It is known that streptomycin when given systemically in adequate dosage diffuses into the intra-ocular fluid in therapeutic concentrations (Leopold and Nichols, 1946). By means of a diffusion experiment similar to that previously described in respect of P.A.S. (Horne and Macaskill, 1950) we determined that therapeutic concentrations of isoniazid were attained in the intra-ocular fluid over a three-hour period in the dosage which was employed in the experiments described below.

I. The Clinical Effect of Streptomycin, Isoniazid and Streptomycin plus Isoniazid in Experimental Ocular Tuberculosis in Rabbits

Methods. A strain of *Mycobacterium tuberculosis*, human type, C.37688, was used and the suspension made as in previous experiments (Macaskill and Weatherall, 1950; Horne and Macaskill, 1951). This was matched against standard opacity tubes and diluted until a suspension containing approximately 15,000 organisms per ml. was produced. Adult mongrel rabbits of

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approximately 2 kg. weight were used. Inoculation into the anterior chamber was made as previously described (Macaskill and Weatherall, 1950). The severity of the lesions produced was assessed by regular clinical examination in life, by post-mortem search for dissemination of the infection, and by histological and bacteriological examination.

Thirty-two rabbits were used and one eye of each was inoculated with the suspension of tubercle bacilli. After twenty-three days, when all eyes showed signs of infection, the rabbits were divided into four groups according to the severity of the lesions. From these groups, rabbits were allotted, by a random procedure, to three treatment groups and a control group as follows:

Group O	.. ..	Controls.
Group S	.. ..	Streptomycin: 30 mg./kg. body weight intramuscularly daily.
Group H	.. ..	Isoniazid: 15 mg./kg. body weight intramuscularly daily.
Group SH	.. ..	Streptomycin plus isoniazid in above dosage.

The severity of the lesions was assessed for a period of thirty-five weeks after inoculation by the method of scoring used in previous studies, the observer being unaware of the treatment which the rabbit had received. Treatment was carried out for a period of sixteen weeks, and the eyes were observed for a further period of sixteen weeks after the cessation of treatment.

Some animals were killed at various stages of the study on account of the severity of the ocular lesion. For this reason all but two of the control animals were killed five weeks after starting treatment. As there was no effective control group thereafter, the study was continued in order to observe the comparison between the treatment groups.

Results. After inoculation of the suspension of tubercle bacilli into the anterior chamber, the ocular lesions followed the same course as described in previous reports (Horne and Macaskill, 1951). After a transient redness lasting one or two days, the eyes became white and were indistinguishable from normal. Seventeen to twenty-one days after inoculation signs of iritis were seen. This was soon followed by the appearance of minute areas of caseation, greater in some animals than in others. Treatment was begun twenty-three days after inoculation, by which time all animals had iritis, and caseation of the iris was present in all but three. The foci of caseation enlarged to about 1 mm. in diameter and in some instances became confluent to form a large caseous mass. In those in which the lesions progressed, the whole anterior segment of the eye became caseous, and when this result seemed inevitable the animal was killed.

The progress of the lesions in the control and treatment groups is shown in Figs. 1 and 2. It will be noted that the average amount of caseation at the commencement of treatment was the same in all groups.

The iritis increased markedly in the control group, whilst the treatment groups fared better. Similar observations were made in respect of the degree of caseation. Five weeks after the commencement of treatment six out of eight of the control group had to be killed on account of the severity of the lesions. In the treatment groups, none of the animals had to be killed in the group treated by streptomycin plus isoniazid, compared with one in the group treated by isoniazid alone and two in the group treated by streptomycin alone.

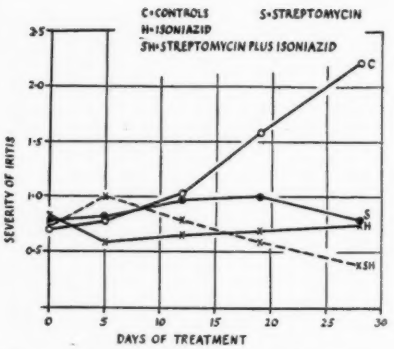

FIG. 1.—Severity of iritis—effect of streptomycin, isoniazid, and streptomycin plus isoniazid.

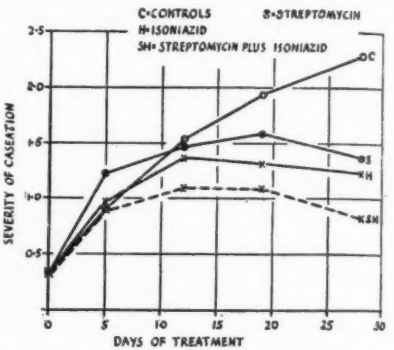

FIG. 2.—Severity of caseation—effect of streptomycin, isoniazid, and streptomycin plus isoniazid.

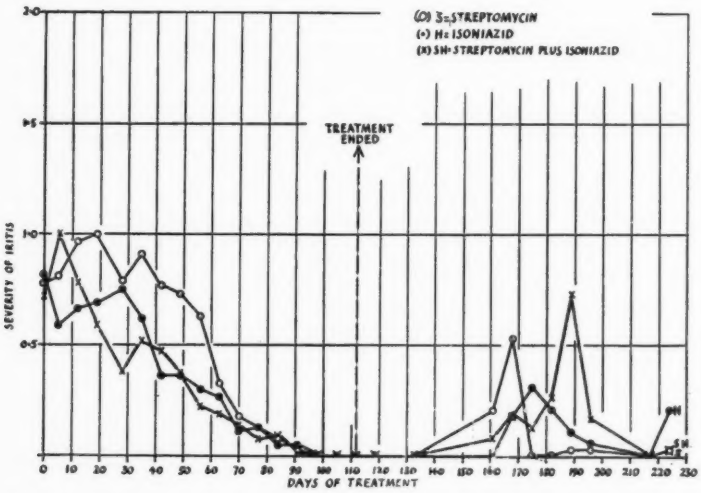

FIG. 3.—Severity of iritis—comparison of effect of streptomycin, isoniazid, and streptomycin plus isoniazid.

The two remaining animals in the control group had to be killed seven and eight weeks respectively after treatment commenced.

II. Comparison of Effect of Streptomycin, Isoniazid and Streptomycin plus Isoniazid

Methods. Treatment as described above was continued in the three treatment groups for a further eleven weeks—sixteen weeks in all. Thereafter the progress of the lesions was observed for a further period of sixteen weeks. All animals were then killed, post-mortem search was made for dissemination of the tuberculous infection and the eyes were submitted to bacteriological and histological examination.

Results. Following chemotherapy there was a reduction in the iritis and caseation of the eye in the three treatment groups (Figs. 3 and 4). After treatment for sixteen weeks, none of the animals showed iritis (Fig. 3). At the completion of treatment, clinical cure—as evidenced by complete disappearance of caseation—had occurred in four out of the eight surviving animals in the streptomycin plus isoniazid group, three out of seven in the isoniazid group, and one out of five in the streptomycin group (Fig. 5). The clinical cure manifested itself by a progressive absorption of the caseation in the iris, the site being demarcated by an indented, atrophic area, paler in colour than the surrounding iris.

There was a recurrence of iritis in some animals in all treatment groups, the earliest being two weeks after cessation of treatment (Fig. 3). Caseation also began to recur in some animals, the earliest recurrence being observed seven weeks after the end of treatment (Fig. 4). At the end of the study, *i.e.*, sixteen weeks after the end of treatment, four animals remained apparently cured in the streptomycin plus isoniazid group, and one each in the groups

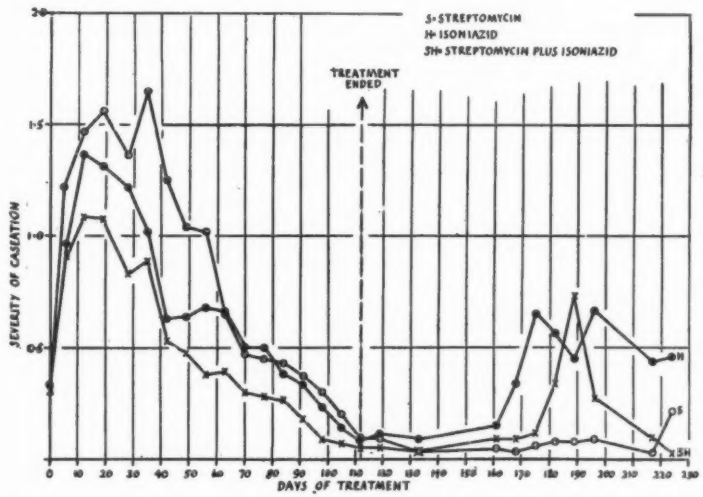

Fig. 4.—Severity of caseation—comparison of effect of streptomycin, isoniazid, and streptomycin plus isoniazid.

treated by streptomycin alone and isoniazid alone (Fig. 5). Furthermore, two animals in the streptomycin plus isoniazid group had had to be killed because of the severity of the lesions, compared with four in each of the other two groups (Fig. 6).

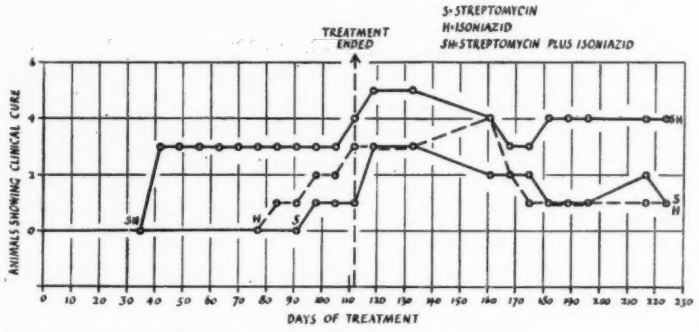

FIG. 5.—Animals showing clinical cure.

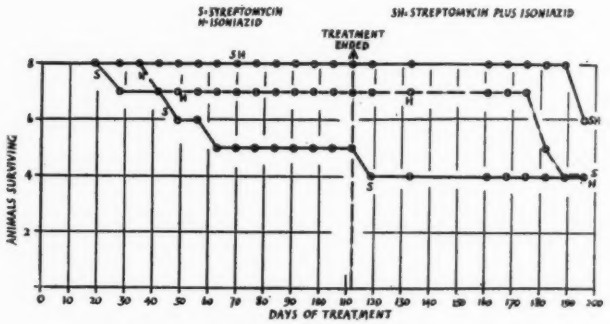

FIG. 6.—Animals surviving at end of experiment.

III. BACTERIOLOGICAL RESULTS

Methods. At necropsy, bacteriological examination of the ocular tissues and of portions of lung, liver and spleen was carred out. In four of the animals in the early part of the experiment intra-ocular fluid only was investigated, but subsequently, and in all of the animals killed at the end of the experiment, one half of the affected eye was submitted for bacteriological examination, the other half being examined histologically. The tissues were macerated by scissors and submitted to acid-alkali concentration. Direct films stained by the Ziehl-Nielson method were examined and cultures, in duplicate, made on Loewenstein-Jensen medium. The cultures were kept for twelve weeks. Resistance tests were carried out by the methods recommended by the Medical Research Council of Great Britain Isoniazid Trials (1953). The medium used in the case of streptomycin resistance tests was that of Davis and Dubos, and in isoniazid resistance tests, Loewenstein-Jensen. Histological sections were also stained by the Ziehl-Nielsen method.

Results. The results are recorded in Tables I and II. It will be observed that tubercle bacilli were found by some method—direct film, culture, or in histological section—in all animals which had to be killed on account of the

TABLE I.—OBSERVATIONS MADE ON OCULAR LESIONS IN TREATED ANIMALS

Treatment group	*Rabbit No.*	*Day killed*	*Bacteriological Results*		*No. T.B. +ve on Culture in surviving rabbits*	*Tubercle Bacilli in histological sections*	*No. T.B. +ve by any method in surviving rabbits*
			Direct film	*Culture*			
Streptomycin	128	19	0	+*		+	
	111	35	0	−*		+	
	101	56	0	−*		+	
	116†	168	+++	−		++	
	110	224	−	+	2	+	3
	112	224	−	−	out of	−	out of
	114†	224	−	+	5	+	5
	134†	224	−	−		−	
Isoniazid ..	130	35	0	C*		+	
	126	175	+	+		+	
	133†	175	+	+		+	
	135	182	+	+	4	+	4
	104	224	−	C	out of	−	out of
	105	224	−	+	7	+	7
	113†	224	−	−		−	
	125†	224	−	−		−	
Streptomycin plus isoniazid	109	189	+	+		+	
	123	189	+	C		+	
	115	196	−	+	3	+	4
	102†	224	−	C	out of	−	out of
	103†	224	−	C	8	−	8
	118	224	−	−		−	
	121†	224	−	−		−	
	124‡	224	−	+		+	

NOTES: C=Culture contaminated. †=Animal clinically cured at some time.
*=Aqueous only. ‡=Animal cured at end of experiment.
O=Not done.

TABLE 2.—BACTERIOLOGICAL RESULTS IN SURVIVING ANIMALS

Treatment group	*No. of Rabbits surviving at end of treatment*	*No. showing clinical deterioration in ocular lesions*	*No. of eyes T.B. Positive*		*No. showing evidence of dissemination (+ve culture)*
			Culture	*Any method*	
Streptomycin ..	5	3	2	3	1
Isoniazid ..	7	6	4	4	1
Streptomycin plus isoniazid	8	4	2	4	1
TOTAL ..	20	13 (65%)	8 (40%)	11 (55%)	3 (15%)

severity of the lesions. Of the twenty animals surviving at the end of treatment, thirteen showed clinical deterioration, and tubercle bacilli were obtained on culture in eight animals, and by any method in eleven animals. Dissemination to viscera occurred in three animals. Table 2 shows that these findings occurred in all treatment groups.

Tubercle bacilli were cultured from ocular tissue in three animals (Nos. 114, 133, 124)—one in each treatment group—in which clinical cure with complete disappearance of caseation had been recorded at some stage. Of the three animals, one (No. 124)—treated by streptomycin plus isoniazid—was assessed as clinically cured at the end of the experiment, yet organisms were isolated from the eye.

Despite the duration of chemotherapy, no evidence of drug resistance was found in any of the cultures. This is in accordance with previous observations regarding the failure of organisms to develop drug resistance in animals treated with anti-tuberculous chemotherapy.

Discussion

From the results recorded above, it seems that treatment by means of streptomycin, isoniazid, or streptomycin plus isoniazid, in the dosage used, is effective in securing regression of established tuberculous lesions of the iris in rabbits. Furthermore, it has been shown that, provided treatment is carried on long enough, apparent clinical cure is possible, with complete disappearance of caseation to leave a depressed atrophic area paler in colour than the surrounding iris: such clinical cure was obtained in each of the three treatment groups. This feature has already been reported by Goulding and Robson (1952) in experimentally induced corneal tuberculosis in the rabbit. The number of animals in each treatment group is too small for definite conclusions to be drawn regarding the relative effectiveness of the treatment groups. The initial rate of healing, however, seemed to be greater in the two groups in which isoniazid was used (Fig. 4), and the employment of isoniazid may be of especial value in ocular disease in view of the importance of bringing the infection under control as quickly as possible to prevent destruction of vital tissues. Treatment with streptomycin plus isoniazid seemed to have the best overall results (Fig. 5) in that four animals in this group remained clinically cured at the end of the experiment compared with one in each of the other two treatment groups. Furthermore, single drug therapy is no longer justifiable in clinical practice because of the readiness with which drug resistance develops —a feature not encountered in this study in animals.

Reactivation of the lesions following cessation of treatment occurred in a significant proportion (65 per cent.) of the animals surviving at the end of the treatment period. Goulding and Robson (1952) state that no recrudescence occurred in their experiment following treatment with streptomycin, isoniazid or a combination of these two drugs. The lesions in this study were, however, of the cornea and not of the iris, and it seems that their animals were killed six weeks after the cessation of treatment—a time when clinical deterioration was beginning to be observed in our experiment. Tubercle bacilli were cultured in eight out of twenty animals surviving in our study. In this respect,

no treatment group fared significantly better than any other. Tubercle bacilli were also cultured from eyes which had been assessed at one stage as clinically cured. Tubercle bacilli were observed on smears or in histological section in three animals in which the organisms could not be obtained on culture. The finding, following chemotherapy, of tubercle bacilli which cannot be grown by existing techniques has been reported in lung lesions resected at operation (Falk *et al.*, 1954): viable tubercle bacilli in such lesions have also been observed (Canetti *et al.*, 1954; Hobby *et al.*, 1954). The discovery of viable tubercle bacilli in 40 per cent. of the eyes following sixteen weeks of chemotherapy suggests that treatment of longer duration is necessary to ensure sterilisation of ocular lesions in the rabbit.

Summary

Tuberculous irido-cyclitis was induced experimentally in rabbits by injection of tubercle bacilli into the anterior chamber of the eye, the effect of treatment with streptomycin alone, isoniazid alone and streptomycin plus isoniazid being assessed by clinical examination, and search for tubercle bacilli at post-mortem examination. Treatment was carried out for sixteen weeks and the surviving animals were observed for a further period of sixteen weeks.

All treatment groups fared better than the controls: those treated by streptomycin plus isoniazid fared better than those in the other two groups.

Of twenty animals surviving at the end of the experiment, tubercle bacilli were found in the ocular lesions at necropsy in eight animals on culture and in eleven animals by any method. Dissemination to viscera was observed in three animals—one in each treatment group.

Tubercle bacilli were cultured from three eyes—one in each treatment group—assessed as clinically cured.

The expenses of this investigation were defrayed by the W. H. Ross Foundation (Scotland) for the Prevention of Blindness; the isoniazid used in this experiment was donated by E. R. Squibb and Sons as "Nydrazid." We are indebted to Miss Sheila M. Stewart for the bacteriological work and to David Hay for considerable technical assistance. The suspension of tubercle bacilli was prepared by Dr. J. R. Duguid.

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DIABETES INSIPIDUS IN ASSOCIATION WITH PULMONARY TUBERCULOSIS

REPORT OF A CASE

By E. H. Horton and D. Roychowdrey

From Glan Ely Tuberculosis Hospital, Cardiff

The syndrome of diabetes insipidus may arise from varied lesions of the hypothalamo-hypophyseal tract. Destruction of the posterior lobe of the pituitary gland, the supra-optic nuclei and the hypothalamo-hypophyseal tract will give rise to symptoms of polyuria and polydipsia provided that the anterior lobe of the pituitary remains intact. The syndrome is a rare one; in some cases the causative factor is determined during life, in others it remains obscure.

Pure polydipsia, completely uninfluenced by treatment with posterior pituitary extract, was observed by Kourilsky in a patient with pulmonary tuberculosis (Kourilsky, 1950). A review of the literature reveals no other similar coincidence of clinical manifestations. Spillane (1952) observed that " ultimate development of tuberculosis is, of course, frequent in sarcoidosis, but it is very improbable that early invasion of the thalamo-pituitary region was tuberculous. Diabetes insipidus occasionally develops as a terminal event in pulmonary tuberculosis."

The case here reported exhibited advanced pulmonary tuberculosis and diabetes insipidus.

Case Report

A steel-works fireman, aged 41, entered hospital as an emergency admission on December 30, 1954. Up to that moment he had been destitute and was living in a Salvation Army Hostel. It was difficult to obtain a history as he was almost moribund, but it emerged that he had been well until four months previously, when he complained of cough and expectoration, polyuria and thirst. These symptoms had become progressively worse and general weakness became marked.

On admission he was found to be a slightly deaf, extremely wasted, almost moribund individual, and the salient features immediately evident were gross finger clubbing and the continuous expectoration of purulent sputum; in addition he was noticed to be passing large quantities of pale urine and to be requesting fluids persistently. On examination, the breath sounds were found to be poor over the left hemithorax and a pleural rub was evident in the left axilla. Bilateral otitis media was present. Fundi normal.

Investigations:

X-ray chest. Extensive bilateral pulmonary tuberculosis was seen with a left-sided fluid containing pneumothorax. This was aspirated and found to contain thick yellow pus, from which no organisms were grown.

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Sputum. Positive for tubercle bacilli and coliform type bacilli.

Urine. S.G. 1002-1006. No abnormal constituents. Output in the first twenty-four hours—212 oz.

X-ray skull; abdomen; hands. Normal.

Sulkowitch test. Normal.

Serum electrolytes. Sodium 135 m.E/litre.
Potassium 3·8 m.E/litre.
Chloride 91 m.E/litre.
Calcium 4·8 m.E/litre.

Serum alkaline phosphate. 14·8 K.A. units per 100 ml.

Thymol turbidity. 4 units.

E.S.R. 44 mm. fall in first hour (Wintrobe).

R.B.C. 4,220,000 per cm. W.B.C. 10,200 per cm. Hb. 116μ. per cent. C.I. 0·9. W.R. negative.

He was treated with streptomycin and isonicotinic-acid hydrazide and chloromycetin. It was ascertained a few days after admission that he had been diagnosed in 1952 as suffering from pulmonary tuberculosis on radiological and bacteriological evidence. He was treated by chemotherapy at another hospital and polyuria was then noted, which responded to pitressin and did not recur when this was discontinued after eight days. On discharge after four months he failed to remain under supervision. (There was no family history of tuberculosis. He himself experienced meningitis at the age of 5, and for many years he had been drinking heavily and persistently.)

Course. The daily output of urine before pitressin was given was 12-17 pints. When pitressin was given, first in doses of 10 units four-hourly, then 20 units four-hourly, this was reduced to between 8-10 pints. Cessation of pitressin led to an immediate rise to the higher figure and the urinary output was never reduced to normal. He continued to expectorate the contents of his empyema cavity, and, though his general condition improved in the first two weeks, it then deteriorated and he died twenty-eight days after admission.

At post-mortem examination (Dr. Leopold, Welsh National School of Medicine), the presence of extensive bilateral fibrocaseous tuberculosis was confirmed, with a left-sided empyema. No other pathological lesions were demonstrated. The brain was normal, macroscopically and microscopically.

Discussion

In this case the diagnosis of pulmonary tuberculosis was soon evident, and various causes of the marked polyuria were considered. Primary renal disease was excluded by the complete absence of abnormal urinary constituents, retinopathy and hypertension. Diabetes mellitus was readily excluded, and the normal serum calcium value and normal Sulkowitch reaction were considered to exclude hyperparathyroidism. Diabetes insipidus was thus considered to be present, but it was not practicable to perform the "smoking test"; neither was it considered advisable to withhold water from the patient in view of his desperate circumstances. The response to pitressin was quite evident in a marked reduction in urinary output, but, as previously stated, this response was not complete on a dosage of 20 units four-hourly.

Spillane (1952), Scadding (1950), have fully summarised the literature concerning the etiology of diabetes insipidus; sarcoidosis, xanthomatosis and syphilis have to be considered, in addition to secondary carcinomatous deposits,

the primary lesion being found most frequently in the breast or in the bronchus. Carcinoma of the thyroid gland, gastric carcinoma, lymphosarcoma, melanoma, hypernephroma, lymphadenoma, reticulosarcoma, prostatic carcinoma, leukæmia, myeloma, have all accounted for occasional cases. There was no evidence of any of those conditions in this case, and no abnormal histological findings were in evidence in the brain. Thus, this case resembles Kourilsky's in that the diabetes insipidus was associated with pulmonary tuberculosis, but the pathological process leading to the development of the diabetes remains obscure. It could hardly be termed a terminal event, as, when the diabetic condition was first diagnosed, the pulmonary lesions were by no means advanced in extent; there remains no evidence to show in what way, if at all, tuberculosis was responsible for the disturbance in the water balance.

Summary

1. A case of diabetes insipidus in association with pulmonary tuberculosis is described.

2. There was partial response to pitressin.

3. The necropsy examination showed no abnormal histological appearances in the pituitary body or hypothalamus.

Our thanks are due to Dr. V. Emrys Jones, Medical Superintendent, Glan Ely Hospital, for permission to publish this case.

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MEDIASTINAL ADENOPATHY SIMULATED BY TUBERCULOUS LUNG FOCI

By R. L. Sadler

From the Chest Clinic, Doncaster.

Pruvost *et al.* (1948) gave examples of radiological *images trompeuses* which had been mistaken for primary complexes of tuberculosis. The commonest source of such an error, in the experience of these authors, was a tuberculous "round focus" of the lung parenchyma—usually sited in the apical segment of a lower lobe.

The following two cases are further examples of adenopathy simulated by tuberculous disease in the lung.

Case 1. A woman of 22 was a recent contact of an open case of pulmonary tuberculosis, and herself had recent chest symptoms and a positive sputum.

The P.A. chest film (Fig. 1) showed two rounded opacities in the left upper lung field. The inner opacity appeared to arise from the mediastinum. The lateral X-ray (Fig. 2) showed that both shadows lay near the hilum, suggesting a primary parenchymal focus with a glandular component.

Bronchoscopy showed no endobronchial evidence of enlarged glands.

A trial A.P. (Fig. 3) failed to convert the sputum although the pneumothorax lung was anatomically free. However, following the induction of the A.P., the inner opacity was seen to have changed position, indicating that it lay within the lung.

A left upper lobectomy was performed at a later date. Both opacities were then seen to be associated with tuberculomata within the resected lobe, and there was no mediastinal adenopathy.

Case 2. A woman of 35 had a sputum containing tubercle bacilli. The P.A. X-ray (Fig. 4) showed a rounded mass adjacent to the right hilum. The presence of a spasmodic unproductive cough, and of a localised rhonchus in the right mid-zone, together with the appearance of the P.A. film, led at the initial examination to a diagnosis of tuberculous adenopathy.

On admission to sanatorium, however, it became evident from the lateral film that the tuberculous lesion lay not at the hilum, but was located at the apex of the right lower lobe.

In an X-ray in the lordotic position (Fig. 5) the focus is seen to lie subjacent to the upper part of the major septum, and its outline appears triangular rather than rounded.

Discussion

To support a diagnosis of hilar glandular enlargement additional X-rays must be taken in all cases (Twining, 1951); and such special view radiographs have also the advantage of demonstrating adenopathy not apparent in a straight film.

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As an example of the second purpose, the paratracheal group of glands may be mentioned. In the investigations of Bentley *et al.* (1954) it was found that about half of the cases with adenopathy at this site had been undiagnosed radiologically in life. When not perceptible in the P.A. film the outline of these glands may be shown within the mediastinal shadow by a high penetration Bucky film (McCourt and Robbins, 1951), by careful interpretation of the lateral radiograph (Engel and Kayne, 1940), or by lateral tomography (Simon, 1953).

Similarly, enlarged glands of the tracheal bifurcation group are never visualised in a P.A. film, being well hidden in the shadows of the heart, great vessels and vertebræ. Engel and Kayne demonstrate how this gland group may be recognised in the right lateral view by its relation to the bronchial tree; McCourt and Robbins detect its hypertrophy from the alteration in contours of the adjacent œsophagus and right main bronchus.

As illustrated in Cases 1 and 2, such special view radiographs are essential also to confirm or refute a diagnosis of mediastinal adenopathy made on the P.A. film.

Summary

Two cases are described in which tuberculous foci in the lung presented similar radiographic appearances to those of enlarged hilar glands.

Special view X-rays are essential to elucidate such cases, as well as to demonstrate adenopathy not apparent in the P.A. radiograph.

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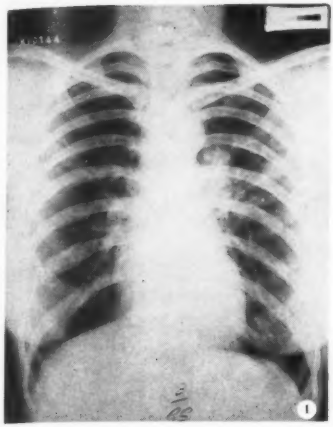

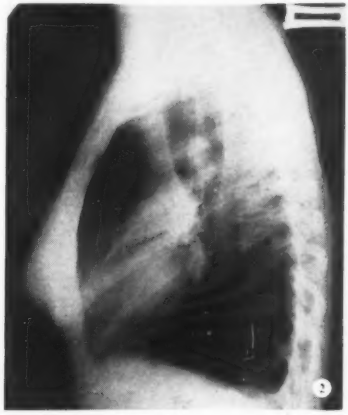

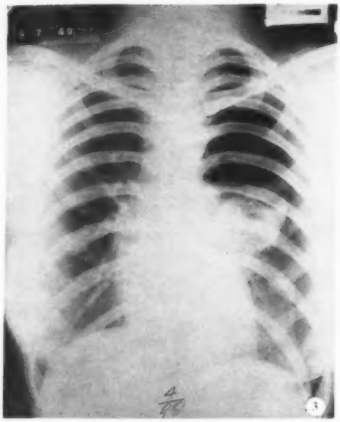

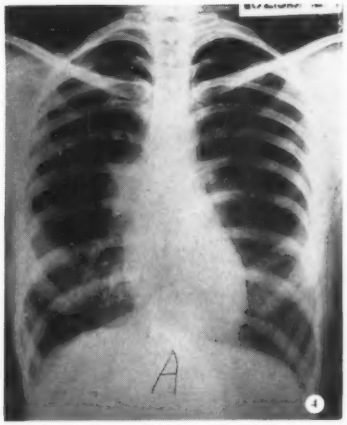

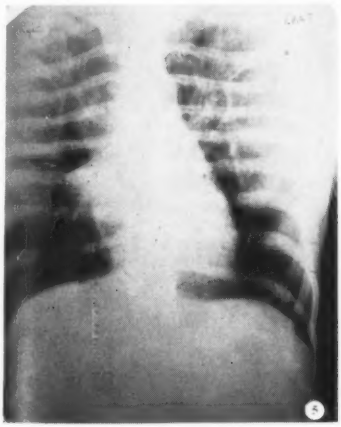

FIG. 1.—P.A. film showing two rounded shadows in left upper lobe, resembling a "primary complex."

FIG. 2.—Left lateral film. Both round opacities are located near to the hilum. Pre-operative film.

FIG. 3.—Following A.P. induction. The inner opacity has moved one rib space downwards, and is therefore intrapulmonary.

FIG. 4.—Rounded opacity of a parenchymatous focus at the apex of the right lower lobe, resembling adenopathy in the P.A. film.

FIG. 5.—Lordotic view shows the same focus as a triangular opacity at the apex of the lower lobe.

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PNEUMOTHORAX OCCURRING AS A COMPLICATION OF ARTIFICIAL PNEUMOPERITONEUM THERAPY

By M. J. Greenberg and P. B. Woolley

From the Chest Clinic, Manchester.

In 1939 Mellies was the first to describe spontaneous pneumothorax as a complication of pneumoperitoneum therapy; subsequently further cases were described by Yannitelli *et al.* (1949), Wynn-Williams (1950), Repa and Jacobson (1951), and Ross and Farber (1951), who reviewed the literature on the subject. Until quite recently all the cases were right-sided with the exception of one described by Smith (1943) which was bilateral and proved to be fatal. In 1954 Howells described two cases occurring on the left side. When the authors first observed this complication it appeared to be a rare one, there being only about twenty cases described in the literature. However, in the past few months at least eight more have been reported and probably there are many more which have not been written up. The reverse complication of pneumoperitoneum occurring during pneumothorax therapy is even rarer and there are only three cases in the literature.

A considerable number of these cases have been associated with the development of an air-containing cyst close to the right diaphragm; this pneumocele, as seen on screening, has tended to enlarge and has finally ruptured into the pleura. Why this should occur predominantly on the right side is discussed later.

At this Chest Clinic four such incidents occurred in three patients over a period of eighteen months; apart from the frequency an unusual feature is the fact that in two instances the spontaneous pneumothorax was maintained as a therapeutic measure.

Case Report

Case 1. V.N., a woman aged 32, had been found to have in April 1951, infiltration in the right lung field and left mid-zone, together with a 5 cm. cavity in the right lower zone. Her sputum was positive for tubercle bacilli. Sanatorium regime and chemotherapy were supplemented in June 1951, by a pneumoperitoneum which was maintained after her discharge from sanatorium with weekly refills of 1,000 c.c. It was noticed, however, that a cyst-like structure had become visible just below the right diaphragm, on a film taken on January 1, 1952 (Fig. 1). In October 1952, the refills were given fortnightly and the patient was up and about all day, quite well and with a negative sputum. On December 2, 1952, the day after her usual refill, she experienced severe right shoulder pain which passed off after twelve hours. No other symptom was noticed. When she was screened, preparatory to a refill, thirteen days later, she had a large right-sided pneumothorax in addition to the cyst; the pneumoperitoneum had completely disappeared (Fig. 2). No

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surgical emphysema was noted. She was admitted to hospital and a thoracoscopy showed a peritoneal herniation through the postero-lateral part of the right hemi-diaphragm. The hernia was covered by a yellowish coat through which small blood vessels could be seen. The appearance was very similar to that of a loop of colon. Just medial to it was an adhesion uniting the diaphragm to the lateral border of the lower lobe of the right lung. The rest of the hemi-diaphragm was healthy. A barium swallow and follow-through showed the gut to be normal. The pneumothorax was allowed to absorb and the cyst disappeared in three weeks.

Case 2. F.S., a man aged 23, was discovered in December 1952, to have a 3 cm. cavity in the right upper lobe and bilateral apical infiltration. He was given streptomycin and P.A.S. and in March 1953, was admitted to sanatorium. A pneumoperitoneum was induced on April 28, 1953, and maintained with weekly refills of 1,000 c.c. of air. Chemotherapy and bed rest were continued. On July 27, 1953, eight hours after the usual refill, he complained of tightness in the chest after a bout of coughing. He was not screened, however, until four days later when no air was visible under the diaphragm and a great deal was present in the right pleural cavity. At thoracoscopy, four weeks later, nothing abnormal was noted about the right hemi-diaphragm but some apical adhesions were divided. No pneumocele had been seen radiologically. The pneumothorax was maintained as a therapeutic measure.

Case 3. E.M., a woman aged 21, developed a left pleural effusion in 1948 from which she made a good recovery. In June 1951, however, she broke down and was admitted to sanatorium with extensive bilateral tuberculous infiltration. After one month's bed rest a pneumoperitoneum was induced and produced marked healing of the lesions. Chemotherapy and further bed rest were continued and after discharge from sanatorium she remained well, sputum negative, and up and about all day. Refills of 1,000 c.c. were given fortnightly on the left side, well below the costal margin. On April 21, 1953, a week after a normal refill, she noticed sudden pain in the right shoulder and back, followed by mild dyspnœa for twenty-four hours. She did not feel unwell enough to inform the Clinic or her own doctor, but, seven days later, screening showed a large right pneumothorax and virtually no pneumoperitoneum. No cyst was seen. On bed rest in sanatorium the air absorbed completely from the pleural space and on May 13, 1953, the pneumoperitoneum was re-induced with 1,000 c.c. of air without any further incident. In September 1953, five months later, a large cystic shadow appeared on the postero-lateral aspect of the right hemi-diaphragm (Fig. 3). Its size did not vary with the position of the diaphragm, nor with the intra-peritoneal pressures. After the patient had been warned that the complication might recur, the pneumoperitoneum was continued uneventfully with fortnightly refills of 1,000 c.c. of air. On February 16, 1954, however, screening showed no air in the peritoneal space, a right pneumothorax and the cyst reduced to half its usual size (Fig. 4). On direct questioning the patient admitted that she had noticed slight dyspnœa seven days previously. At thoracoscopy a sausage-shaped cyst 2 inches by 1 inch was seen lying on the postero-lateral aspect of the right hemi-diaphragm. It was apparently covered by a glairy, œdematous parietal pleura and was traversed by a narrow band of yellowish white tissue. This cyst disappeared on April 21, 1954. This time the pneumoperitoneum was abandoned and the pneumothorax was maintained as a therapeutic measure. It is still being continued.

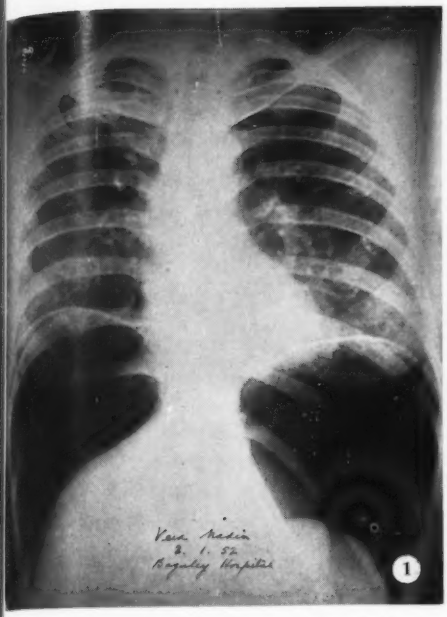

FIG. 1.—Showing cyst-like structure visible just below the right diaphragm.

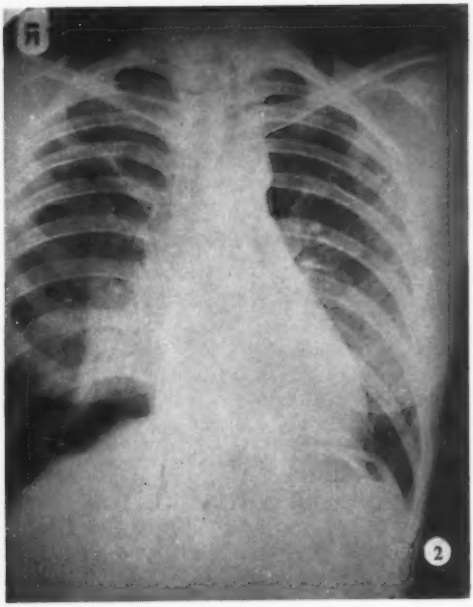

FIG. 2.—The pneumoperitoneum has completely disappeared and there is now a right-sided pneumothorax in addition to the cyst.

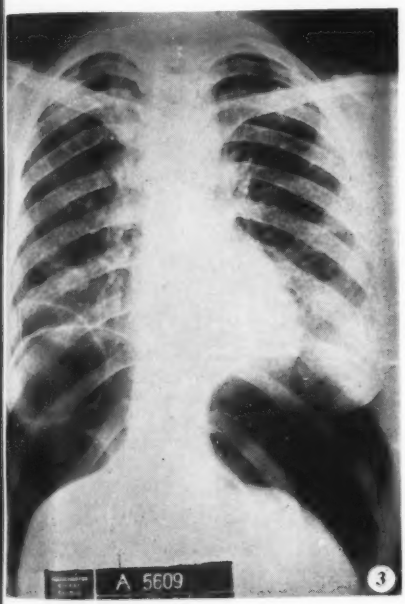

FIG. 3.—Large cystic shadow on the postero-lateral aspect of the right hemi-diaphragm.

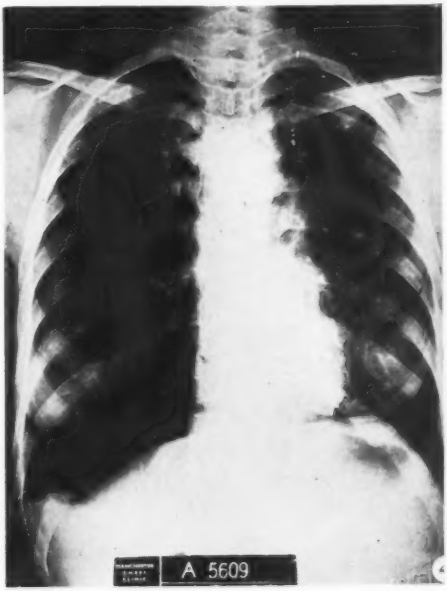

FIG. 4.—Pneumoperitoneum has disappeared, but a right pneumothorax is present and the cyst is reduced to half its usual size.

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Discussion

Various theories have been expounded to explain the development of pneumothorax complicating pneumoperitoneum therapy. One of the first was that of Banyai and Jurgens (1940), supported by Simmonds (1946), which suggested that the air entered the thorax via the aortic or œsophageal hiatuses into the mediastinum, and then ruptured into the pleural space. If this theory were tenable one would expect signs and radiological evidence of mediastinal emphysema; this has only rarely been reported. Secondly, with mediastinal emphysema one would expect at least an equal number of pneumothoraces to occur on the left side. The radiological development of a pneumocele or observation of a direct communication through the diaphragm—as in the cases above—also tend to disprove this theory.

Spencer Jones and Yuill (1952) have suggested that two types of case exist, those due to a congenital defect and those due to trauma. The former probably develop quickly on the induction of the pneumoperitoneum, whereas with the latter there may be a considerable delay between the induction and the complicating pneumothorax. The traumatic variety—due really to a sudden increase in intra-abdominal pressure—is probably the commonest and is associated with weakness or hypoplasia of the diaphragmatic musculature. The increased abdominal pressure would force the peritoneum through the gap so that the overlying pleura would be raised to form a bleb or cyst.

The high incidence on the right side is probably connected with the presence of the liver. Johnson (1954) has suggested that excessive pressure on the right diaphragm may result from a piston-like action of the liver when it moves upwards following a sudden increase in intra-abdominal pressure. A second and more probable explanation is that of Guillaudau and Stewart (1954). They believe that the air of the pneumoperitoneum separates the liver from the diaphragm, with the result that the liver becomes suspended from the diaphragm by its ligaments. In its descent the liver rotates and this is followed by an increased tension on these ligaments, particularly the right triangular one. This abnormal tension may separate some of the diaphragmatic fibres at the posterior and lateral attachments of this ligament.

Therapeutic paralysis of the phrenic nerve has been suggested as a factor in weakening the diaphragm, but it was not performed in any of the three cases described, nor in many of the other cases reported. In conclusion it would seem that localised weakness, together with indirect trauma, is the main factor responsible for the three cases which have been summarised above. Although these pneumothoraces have not led to any untoward complications, it would appear advisable to abandon pneumoperitoneums as soon as a cyst-like structure becomes visible in the neighbourhood of the diaphragm.

Summary

1. Three cases of spontaneous pneumothorax complicating pneumoperitoneum therapy are described. They occurred during a period of eighteen months at a large chest clinic.

2. The theories of causation are discussed.

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SPONTANEOUS HÆMOPNEUMOTHORAX

WITH REPORT OF A CASE

By R. A. L. Agnew

From St. Richard's Hospital, Chichester.

Spontaneous hæmopneumothorax is an uncommon condition. About 150 cases have been recorded in the literature up to 1954 (Calvert and Smith, 1955). It is generally accepted that the majority of cases of the so-called benign or idiopathic type of spontaneous pneumothorax are due to the rupture of a subpleural cyst or bulla (Maxwell, 1954). The accumulation of air in the pleural cavity may give rise to torn pleural adhesions (Ross, Dugan and Farber, 1953). The parietal ends of these adhesions may continue to bleed, as they are supplied by the intercostal arteries, and are, therefore, uninfluenced by the staunching effect of the collapsing lung on the visceral ends (Hartzell, 1942).

It may be difficult to determine the onset of hæmorrhage in a spontaneous pneumothorax in the absence of the classical signs and symptoms of shock, and for this reason diagnostic aspiration of a small amount of any accompanying pleural effusion has been advocated (Dubose, Price and Guilfoil, 1953). These workers stress close observation of the patient for signs of bleeding and the replacement of blood loss by transfusion. If bleeding is rapid and uncontrolled, they advise open thoracotomy, in order to find the source of the hæmorrhage. They emphasize that "in any patient with spontaneous pneumothorax who is in collapse when first seen, or who suddenly goes into this state, massive intrapleural hæmorrhage must be considered."

The symptoms may at times closely simulate those of a perforated peptic ulcer or acute myocardial infarction, and the patient may be in danger of exploratory laparotomy (Kjaergaard, 1932).

It is thought that the following case should be reported as it illustrates some of the above points.

Case History

B.T., a 41-year-old manager of a sports shop, was admitted to St. Richard's Hospital for thoracotomy on 14.7.54, from another hospital.

At 8 a.m. on 27.6.54 he was tying his shoe-lace with his right foot raised on a chair, when he felt a pain across the middle of his chest. Breathlessness was not noticed until walking up a hill about one hour later, and this became progressively worse, and resulted in his admission to hospital about 1 p.m. On admission he still had pain across the lower end of the sternum on deep inspiration and was found to have diminished breath sounds over the front of the chest on the right side, with a resonant percussion note. The trachea was central, though the apex beat was displaced to the left. A tentative diagnosis of spontaneous pneumothorax was made, but perforated peptic ulcer was considered, and an electro-cardiograph was done to rule out cardiac infarction.

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At 5.20 p.m. the trachea was definitely displaced to the left and by the following day he had clearly developed a tension pneumothorax. 1,400 ml. of air under positive pressure were withdrawn from the right pleural space. Chest X-ray had shown complete collapse of the right lung with mediastinal displacement to the left. A further aspiration of 1,000 ml. air was done on 29.6.54. He remained well clinically until 4.7.54, when he developed a right-sided pleural effusion with radiological evidence of fluid to just below the level of the clavicle. It was decided to treat him expectantly, but diagnostic aspiration on 8.7.54 revealed a heavily blood-stained pleural fluid. Culture of this fluid for six weeks showed no growth of tubercle bacilli and repeated sputum examinations were also negative.

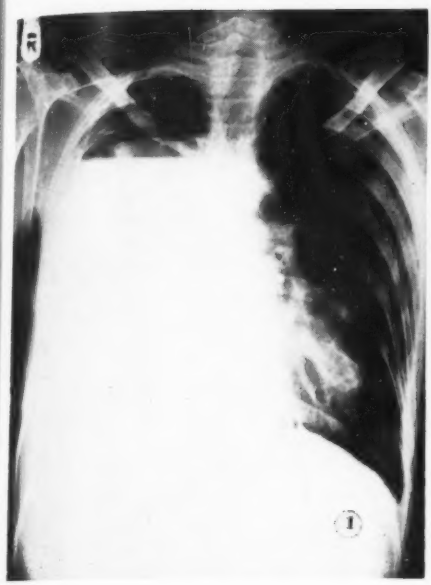
Aspiration was repeated on 9.7.54, but had to be stopped after the withdrawal of 4 oz. deeply blood-stained fluid owing to the distress of the patient. He continued to be gravely ill with marked dyspnœa and pain in the upper lumbar region, requiring oxygen, morphine and pethidine for relief. He was sweating, had a persistent pyrexia of 99°-102° F. and a tachycardia of 116-124/min. On 12.7.54, 1,000 ml. air under positive pressure and 30 oz. heavily blood-stained fluid were withdrawn with temporary relief of symptoms. Pulse rate remained about 120/min., however, and 32 oz. blood-stained fluid were aspirated from the right pleural cavity the next day. A further 10 oz. were withdrawn on the morning of his transfer to St. Richard's Hospital, with a diagnosis of bleeding from a torn pleural adhesion, or hæmangioma. Examination showed a very ill, pale, dyspnœic man, rather underweight for his height. Chest X-ray showed the right hæmopneumothorax with a fluid level just below the clavicle (see Fig. 1).

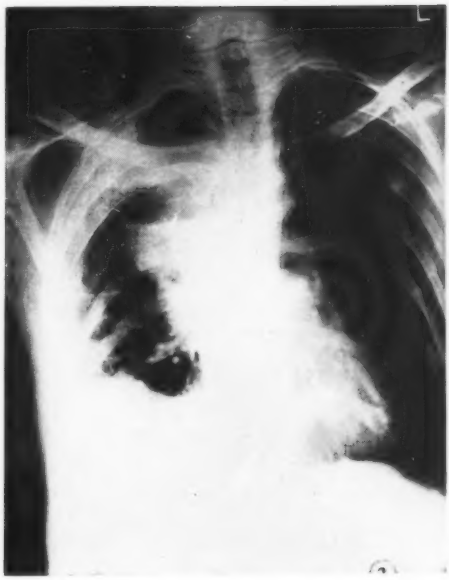
There was no past history of a similar episode and none of pneumonia or asthma. In fact he was so healthy in the past that he had been a paratrooper in World War II with seven jumps to his credit.

Shortly after admission, Mr. V. T. Powell performed a right thoracotomy under general anæsthesia. The seventh rib was removed and about 3 pints of blood-stained fluid and clot were removed from the right pleural cavity, and an incomplete lung decortication carried out. There was an adhesion near the internal mammary vessels on the right, rupture of which may have been the cause of the bleeding. The lung re-expanded about 75 per cent. and a drainage tube was left in the tenth space posteriorly, and connected to an underwater seal. He was bronchoscoped while in the theatre, but no evidence of carcinoma was found. Hæmoglobin had been 80 per cent. (Haldane) pre-operatively, so 2 pints of whole blood were transfused during and after operation.

By evening of the same day his general condition was excellent. A total of 4,200 ml. air and 32 oz. of blood-stained serous fluid was removed from the right pleural space by aspiration and drainage at intervals from the first to tenth post-operative days. Screening on 23.7.54 showed only a thin fluid level, but the right lung was slow to re-expand fully, owing to persistent bronchopleural fistula.

On 30.7.54 an intercostal catheter was inserted into the second right interspace anteriorly through a thoracoscopy cannula and connected to an underwater seal. This was continued for forty-eight hours and then disconnected, a check X-ray showing further re-expansion of the right upper and lower lobe. On 1.8.54 (eighteenth post-operative day) he developed a high swinging temperature and tachycardia, and looked extremely ill. He was started on oral Chlortetracycline (" Aureomycin ") and during the next two days there was a partial improvement clinically. On 4.8.54 an empyema pocket under the





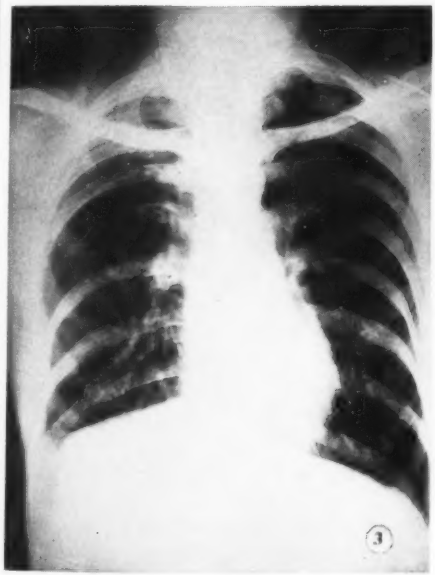


FIG. 1.—Right hæmopneumothorax with fluid level to just below the clavicle.

FIG. 2.—Showing the empyema pocket under the second right rib, which developed following closed thoracotomy.

FIG. 3.—X-ray taken on 9.12.54 showing absence of fluid and air. Note the height of the right side of the diaphragm.

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right second rib anteriorly was diagnosed (see Fig. 2) and 2 oz. of fibrinous yellow fluid were aspirated. One mega unit crystalline penicillin was instilled into the empyema space immediately following this aspiration.

The following day there was a dramatic clinical improvement, the patient's temperature being down to normal, and he was sitting up and able to do breathing exercises. About 10 ml. fibrinous slightly blood-stained fluid was removed the same day from the first right interspace anteriorly, and again 1 mega unit of crystalline penicillin was instilled.

Screening on 7.8.54 showed marked re-expansion of the right lung, all traces of fluid having disappeared from in front, though there was still obliteration of the right costo-phrenic angle. On 12.8.54, Chlortetracycline was discontinued and 600 ml. air were removed from the right apical pleural space, posteriorly, and a further 150 ml. air from the same site four days later.

By 23.8.54 (forty days after his initial thoracotomy) he was feeling very fit and was up and about the ward all day. Screening showed no air space visible, but the right diaphragm appeared paralysed.

He was discharged on 26.8.54 and has been seen in the Out-patient Department on four occasions since. The first was on 9.9.54, when X-ray and screening showed a small quantity of air at the right apex; the right diaphragm was still immobile. This air had been completely absorbed by 7.10.54, when he was back at work and feeling well. He looked fit and had put on over a stone in weight since operation, weighing 8 stone 1 lb. On 9.12.54 he reported he was doing a full day's work, with no pain in the chest, no sputum or hæmoptysis, and that his weight was remaining constant. Chest X-ray (see Fig. 3) showed only a little residual pleural thickening on the right side, and it was noted that the diaphragm did not appear sufficiently elevated for it to be paralysed.

Screening on 14.4.55 showed the right diaphragm to be moving well and chest X-ray confirmed the presence of pleuro-diaphragmatic adhesions as the probable cause of its previous immobility. Clinically he remained very fit and reported he was doing more gardening than ever before.

Discussion

One of the earliest references to the treatment of hæmothorax is that in which Laennec (1819) in dealing with effusions resulting from penetrating wounds of the chest says: "The most rational indication is to confine the blood within the chest, so as to make it compress the lung and thereby check the hæmorrhage if possible."

In more recent times, Maxwell (1938) advocates leaving the blood alone for one week in order to avoid further hæmorrhage before the bleeding point is sealed off. He recommends, however, that an attempt should be made to remove it as completely as possible after that time before permanent organisation takes place. Sellors (1945) claims that immediate thoracentesis does not restart bleeding and agrees that fibrothorax should be avoided by repeated aspirations. If necessary, trypsin (McCroskey and Hardin, 1953) or combinations of streptokinase and streptodornase (Calvert and Smith, 1955) may be used to aid fibrinolysis. Ross (1952) draws attention to the fact that a mortality rate of 25 per cent., in the cases reported up to that time, is high for bleeding from a small vessel, and is in favour of more active treatment should hæmorrhage continue.

In cases of massive intrapleural hæmorrhage, as in one of Calvert and

Smith's patients, delay in thoracotomy may result in a moribund patient too shocked to stand prolonged aspiration. They emphasise that an increasing pulse rate, in spite of normal blood pressure, is a valuable guide to early thoracotomy.

In the present case, preliminary diagnostic aspiration of the right-sided pleural effusion might have enabled the diagnosis to have been made at an earlier date, though whether this would have changed the subsequent treatment is a matter of opinion.

Bronchopleural fistula is a complication of pulmonary decortication mentioned by Deucher (1950) and occurred in the case under discussion. An intercostal catheter was inserted, and this was followed by the development of a small empyema. The latter responded dramatically to aspiration and penicillin replacement, and to oral Chlortetracycline ("Aureomycin"). This was particularly satisfactory in view of the alleged lack of synergism between these antibiotics (Ronald, 1955).

The immobility of the right diaphragm for three months after operation gave rise to some anxiety, in spite of the negative bronchoscopic findings, but its restoration to good movement, nine months after thoracotomy, excluded carcinoma as a cause.

Summary

A case of spontaneous hæmopneumothorax is reported and the treatment is briefly discussed with reference to modern views on the subject.

I am indebted to Mr. V. T. Powell, F.R.C.S., Consultant Thoracic Surgeon, and Dr. J. D. Whiteside, Consultant Physician, St. Richard's Hospital, under whose care the patient was admitted, for helpful advice and criticism, and to Mr. D. G. Martin, F.R.C.S. (Ed.), Surgeon Superintendent, St. Richard's Hospital, for permission to report. I would also like to acknowledge the valuable secretarial assistance of Miss C. Walden.

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AGENESIS OF THE LUNG

By D. Levy

From Peppard Chest Hospital, Oxon.

The rarity of agenesis of the lung is shown by the fact that up to 1951 only 85 cases have been recorded. Although this condition has been recognised as a curiosity of morbid anatomy for over a century, the first recorded diagnosis in life was not made until 1885 (Münchmeyer). During the next fifty years no other living case was reported, but in the last two decades more have been recognised. Wexels (1951) described two examples and reviewed the literature.

The following report gives details of a further case diagnosed during life.

Case Report

A girl aged 8 years had been the subject of a normal pregnancy and birth. At the age of 2 she had a pyrexial chest illness, thought to be whooping cough, from which she recovered completely. At 5 she had measles without chest complication. During childhood she has had no symptoms except on running, when dyspnœa with some wheezing has occurred.

At the age of 7 routine medical examination at school revealed a dorsal scoliosis, for which she was referred to an orthopædic clinic. In December 1954 a pulmonary abnormality was noted on X-ray during an orthopædic review and she was referred for further investigation.

On admission to hospital in January 1955 she had no symptoms. Her general condition was good. There was no finger clubbing. The spine showed a slight dorsal scoliosis convex to the right and the left shoulder was a little depressed.

Examination of the front of the chest revealed slight flattening on the left, but movement was equal on both sides. The trachea was central. The percussion note was impaired over the left lower and mid-zones and normal over other areas. Auscultation revealed reduced air entry and vocal resonance over the area corresponding with impaired percussion; vesicular breath sounds were heard over the right lung and left upper zone.

The heart rate was 80 and regular. A diffuse pulsation was visible to the left of the sternum, but the apex beat was situated posteriorly and was readily palpable when the inferior angle of the scapula was raised. The heart sounds were normal. Examination of the abdomen and central nervous system revealed no abnormality.

Blood: Hb. 86%. W.B.C. 8,600. Sedimentation rate 8 mm. in 1 hour (Westergren). Mantoux test: 1 : 1000 negative. Vital capacity 1,600 c.c.

Chest X-ray showed a cervico-dorsal scoliosis and narrowing of the upper five intercostal spaces on the left side. The left lung field was opaque below the level of the third rib anteriorly. The right border of the heart was drawn completely to the left side of the vertebral shadow.

Tomograms of the mediastinal area clearly showed a right bronchial tree but no evidence of a left main bronchus.

(*Received for publication June* 17, 1955.)

Bronchoscopy revealed a trachea with an unusually narrow lumen, through which only an infant pattern instrument could be passed. There was no evidence of a carina and the orifice of the one bronchial tree corresponded to a right lung arborisation. A bronchogram performed at the same time confirmed the findings. The left bronchus was absent. The anterior segment of the right upper lobe bronchus and the medial division of the middle lobe bronchus were seen crossing the mid-line, to occupy part of the left hemithorax. Barium meal X-ray showed deviation of the œsophagus to the left; the stomach was in the normal position.

Discussion

Agenesis of one lung often occurs in association with other congenital abnormalities, particularly of the heart. The pulmonary vessels necessarily show departure from the normal in regard to their presence, size and anatomical relationship to the other thoracic structures. Patent foramen ovale and patent ductus arteriosis are the commonest associated findings.

Three grades of agenesis are recognised, according to the anatomical classification of Schneider (1912):

Group	*Bronchus*	*Incidence*
I	Complete absence	More common
II	Bronchial bud present	More common
III	Bronchial bud ending in a fleshy structure	Rare

There is no difference in sex incidence, but the left lung is absent more often than the right. The pathogenesis is discussed by Ferguson and Neuhauser (1944), who consider the condition to be a true congenital maldevelopment because of the frequent associated abnormalities.

Agenesis of one lung is compatible with a normal existence and absence of symptoms, and hence may escape notice. Dyspnœa and wheezing on exertion may be found. This is presumably due to obstruction to the tidal air in a narrow trachea, consistent with a group I type of agenesis, as illustrated by the present example. A history of chronic infection is noticeably absent. When acute infections do supervene respiratory embarrassment will be more severe than in the normal chest.

On physical examination the following are characteristic findings. Owing to the unchecked early fœtal development of one lung, the degree of skeletal asymmetry is small compared with the change produced by long-standing pulmonary collapse or fibrosis. The trachea is central. The heart shows gross rotation as well as displacement to the affected side and, as pulmonary herniation also occurs, normal air entry may be heard in both halves of the chest. The percussion note is impaired over the area corresponding to the displaced mediastinum and the rotated heart. If the condition is borne in mind, the history and physical examination may be diagnostic.

Diagnostic aids include the use of various radiographic procedures and bronchoscopy. Postero-anterior X-ray films reveal the picture already described. The raised hemi-diaphragm, narrowing of the intercostal spaces on the affected side, an abnormal cardiac shadow and pulmonary herniation should be noted. Tomograms of the mediastinum, in this instance, were found to be most effective in revealing the bronchial abnormality in the region of the

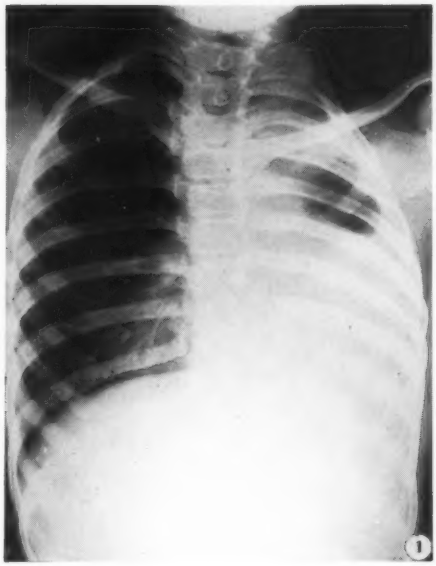

FIG. 1.—Postero-anterior radiograph shows typical appearance of agenesis of left lung.

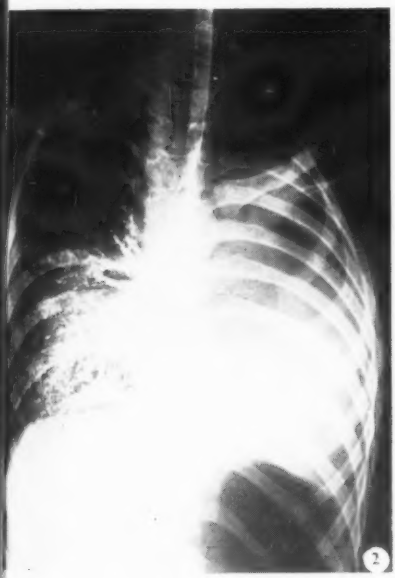

FIG. 2.—Postero-anterior bronchogram demonstrates appearance of right bronchial tree.

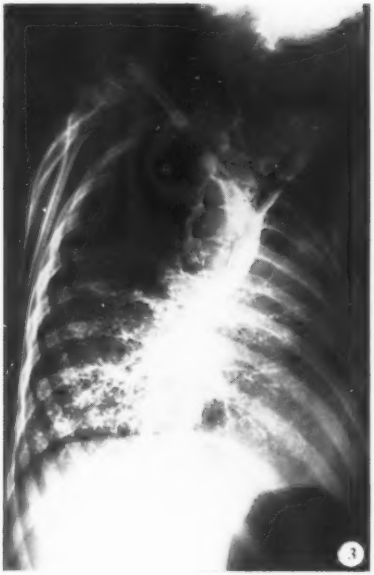

FIG. 3.—Left anterior oblique bronchogram demonstrates branches of right bronchial tree extending into left hemithorax.

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normal bifurcation of the trachea. Barium swallow will show the accompanying œsophageal deviation. Bronchography confirms the diagnosis and the exact state of the bronchial tree. Direct inspection by bronchoscopy will also enable the degree of abnormality to be seen.

When the right lung is missing, dextrocardia may be simulated. Persistent atelectasis in the neonatal period or during infancy may resemble agenesis but is usually associated with recurrent symptoms of respiratory infection. Later in life, total collapse or fibrosis of one lung may bear a superficial resemblance.

Radiologically an exactly similar appearance is produced after pneumonectomy.

When death occurs in early childhood, as it does in a high proportion of cases, it is due to associated gross congenital lesions of other organs. Severe respiratory infections, spontaneous pneumothorax or neoplasm, have a more serious prognosis than would be the case in the normal individual. However, experience with subjects of pneumonectomy suggests that the condition is compatible with a normal existence provided no complication ensues.

Summary

A case of agenesis of the left lung is described.

The etiology, clinical and radiological features are reviewed.

I wish to thank Dr. Harley Stevens, Physician Superintendent, Peppard Chest Hospital, under whose charge the patient was investigated, for advice and permission to publish this case; Dr. G. H. Shaw, Chest Physician, Berkshire Chest Clinic, who referred her with a provisional diagnosis of agenesis; Dr. R. Leatherdale, who performed the bronchoscopy and bronchograms under general anæsthesia; and Dr. P. Cave for radiological reports.

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REVIEWS OF BOOKS

Tuberculosis: Classification, Pathogenesis and Management. By MILOSH SEKULICH. London: William Heinemann (Medical Books) Ltd. 1955. Pp. ix+316. 50s. net.

This book is mainly devoted to the classification of cases of pulmonary tuberculosis. It is elementary knowledge that a case may be either acute or chronic; active, quiescent or temporarily arrested; the sputum may or may not contain tubercle bacilli; the lesions may be localised or diffuse; exudative, caseating, cavernous, fibrotic or calcified.

Of the various classifications which have been proposed I find those of Inman and of Sir Robert Philip as useful as any. But these classifications are not mentioned in this book.

Dr. Sekulich has clearly devoted a very considerable amount of thought and time to this work, in which he aspires to have evolved a classification of pulmonary tuberculosis to end all classifications. If he has done so he is to be congratulated; time will show. His classification, to quote his own words, " . . . consists essentially of the following two types and four forms, the latter of which can be subdivided into numerous subforms; and various particulars of extent and activity are added according to the purposes in view:

I. PRIMARY TYPE
   1. Inflammatory Form (Benign Primary).
   2. Caseous Form (Malignant Primary).

II. SECONDARY TYPE
   1. Fibro-caseous Form.
   2. Fibrous Form."

Dr. Sekulich devotes the latter part of the book to the management of the disease. He says: " In any case of tuberculosis the first essential is to differentiate the primary type from the secondary type of disease." Further, he now asserts that " logical management depends upon the correct classification of each individual case." This seems to savour too much of mechanised medicine—classify the case and apply the treatment laid down. There is more, however, in the treatment of pulmonary tuberculosis than this. Each case is an individual problem, irrespective of the particular niche it may occupy in any subdivision. The psychological aspect is of enormous importance and this cannot be included in any classification. I have found the classification of pulmonary tuberculosis of little value in practice—in fact, classifications appear to be devised to provide work for clerks in offices.

Fifty shillings is a large price to pay for this small book.

G. E. BEAUMONT.

An Historical Chronology of Tuberculosis. By RICHARD M. BURKE. Springfield, Illinois; Charles C. Thomas (Published British Commonwealth: Blackwell Scientific Publications). 1955 (2nd Edition). Pp. xiv+125. 27s. 6d.

The first edition of this useful little book was published in 1938. It consisted of 60 pages of text, 10 pages of bibliography, a large synoptic chart, and an index. The text followed the chronological sequence from the earliest times until the date of publication, and the discoveries or conditions recorded

were set out in very abbreviated form. In this second edition the text is slightly amplified, though it occupies more pages owing to a reduction in the column width. The bibliography is now extended to 30 pages, and the synoptic chart, which was of doubtful value, is now excluded.

A comparison of the texts of the two editions shows that Professor Burke has taken the trouble to carry out a thorough revision. In several instances an entry has been correctly transferred to another year, a few entries relating to events which are now seen to be of secondary importance have been excluded, and some forenames have been altered. The first edition contained quite a number of historical incidents, such as the Battle of Waterloo and Fulton's invention of the steam-boat, which bear no relation to the history of tuberculosis. Some of these have now been excluded, but others still remain. While the bibliography has been carefully prepared, and will be very valuable, there are signs that the author is not completely familiar with the literature on the older work; references are sometimes given to secondary sources and the primary sources are not mentioned. Fernel appeared in the first edition, but he is now excluded, although there is a recent paper on his views on tuberculosis, which had a wide influence. The year of invention of the compound microscope is stated rather too dogmatically. The name of Nielsen, always coupled with that of Ziehl, is now excluded. It would have been better to have printed Greek words in italics rather than in Greek type which frequently shows errors.

These are minor criticisms. This second edition will be welcomed, and the book will be useful both to tuberculosis workers and students for its clear statement of facts and for the detailed references to papers.

E. Ashworth Underwood.

The Health Visitor and Tuberculosis. By Sheena H. Buchanan. London: N.A.P.T. 1955. Pp. 150. 8s. 6d.

Having read with interest and admiration the publication " The Health Visitor and Tuberculosis," the following comments occur to me. After twenty years of Tuberculosis Visiting I remain firmly opposed to combined Health Visiting. On the one hand, many practising Tuberculosis Visitors do not possess the necessary qualifications for Health Visiting, while on the other many Health Visitors have very little, if any, experience of the treatment, care and after-care of tuberculosis—perhaps two to four weeks in a Chest Clinic as a student Health Visitor.

Tuberculosis is an absorbing subject that requires expert knowledge of the disease and its treatment. One of the most important sections of such work is care and after-care in the patient's own home. Away from hospital, where constant medical and nursing supervision was available, a patient is beset with fears for his future; it is at this stage that the Tuberculosis Health Visitor is able to encourage, advise and, in fact, assist the patient to readjust his future. Drugs have contributed much to the treatment of this disease, but on the social, financial, housing and rehabilitation side, a great deal remains to be done. Among these requirements are: (*a*) Ever closer co-operation with the General Practitioner; (*b*) Closer liaison with factories' Welfare Sections—this could be made more possible with the expert training of an Almoner; (*c*) Free discussion with senior members from all Welfare sections of the local authority, who should pool their problems; (*d*) Attendances of the Health Visitor at all Clinic sessions, so that she can have a complete picture—clinical, radiological and therapeutic—and can discuss the social side with the Chest

Physician. This does not always occur where there is a Clinic Sister; (*e*) Now that Chest Clinics are so closely linked with general hospitals, it should be possible for student nurses to be seconded for part of their training to the adjacent Chest Clinic, there to gain training under the supervision of the Tuberculosis Health Visitor, and possibly to be eventually recruited for this fascinating work.

Finally, I would emphasise that efficient, combined Health Visiting is a physical impossibility in thickly populated industrial areas. Moreover, there is much in favour of a Senior Tuberculosis Health Visitor supervising her own team, keeping an already divided section of Public Health in closer unison, and thereby linking Clinic and district or local authority and Regional Hospital Board.

F. M. WILLIAMS, S.R.N., Brom. Cert.

Studies in Tuberculosis. By R. G. FERGUSON. Toronto: University Press (London: Geoffrey Cumberlege). 1955. Pp. xi+124. 28s.

Over a period of years studies in tuberculosis have been made by members of the staff of the Saskatchewan Anti-Tuberculosis League, of which Dr. Ferguson was formerly Director of Medical Services. Upon this valuable work the author has based a series of treatises; and in this interesting book he is concerned mainly with matters related to the epidemiology of the disease.

Racial Susceptibility, Dose in Natural Infection, Effects of Population Movement, are examples of subjects considered. Of particular interest is the first-hand description of the ebb and flow of the tuberculosis epidemic among a primitive population—the Qu'Appelle Valley Indians.

Understanding of the factors involved in the natural decline of the epidemic provides a rational basis for the development of a preventive programme; and in the final chapters the author shows how the deductions of his studies are applicable to this end.

This little book is very readable and likely to be most stimulating to anyone interested in the social aspects of tuberculosis. Its limitation is that the data discussed are mainly derived from a single Province.

R. L. SADLER.

Asthma bronchiale. By Fr. WYSS. Stuttgart: Georg Thieme Verlag. 1955. Pp. viii+120. Illus. D.M. 17.40.

The author, himself an asthmatic subject, according to the preface, has investigated the respiratory dynamics in normal and asthmatic persons. He has taken great pains to determine particulars of the air-current in the bronchial tree and its effect on the respiratory tissue. Graphs and figures illustrate this and especially the resistance met with in asthma. They show clearly the difference between respiration in normal and asthmatic subjects. The fact that the measurements could not be taken in the tubes themselves, but that results had to be calculated from circumstantial evidence, does not diminish the significance of the work. We know more about the flow of air in the bronchial system, but since the bronchial tree is not composed of rigid tubes the laws he has deduced cannot be applied without reservation.

Nevertheless, the publication must be considered a valuable contribution to our knowledge of asthma, and we can profit from the results the author has obtained.

S. ENGEL.

REPORTS

TORONTO HOSPITAL

THE 51st Annual Report for the year 1944 is of considerable interest, especially in relation to recent trends in the treatment of tuberculosis, which presumably is representative of such treatment throughout Canada. We quote, therefore, certain general remarks made by Drs. J. L. Blaisdell, H. S. Coulthard, K. F. Davis, D. R. Garrett and C. A. Wicks, which will be of interest to our readers in relation to:

Rest. Certain trends within recent years resulting in a greater number of patients admitted without symptoms and a more rapid disappearance of symptoms among others has materially lessened the number of our patients for whom we prescribe "total bed" rest. The average exercise category for patients has shifted to the right (toward increased activity). Nevertheless, we have not abandoned the principle of recumbency in bed for varying periods during each day in the treatment of patients with active pulmonary tuberculosis.

Drug Therapy. We continue to use for most patients the following three agents concurrently in the dosage schedule as shown opposite each agent: Streptomycin—1 gramme intramuscularly twice weekly. PAS—10 grammes (14 grammes of the sodium PAS) orally daily (in three or four divided doses). Isoniazid—300 mg. orally daily (in three divided doses). It is recognised that concurrent administration of the three most useful antimicrobial agents in tuberculosis is not practised at many centres because of the understandable desire on the part of many clinicians to reserve at least one of such agents for use if and when deemed necessary. We are not yet fully convinced that significant resistance does develop with concurrent three-drug therapy to a degree making this "triple drug" therapy inadvisable—and we are not at all certain that such resistance reported by the laboratory necessarily involves a lack of clinical effectiveness paralleling the reported resistance.

Collapse Therapy. Because of the apparent efficacy of long-term chemotherapy in treating reversible disease, the use of collapse therapy (artificial pneumothorax, artificial pneumoperitoneum and thoracoplasty) at this sanatorium has continued to decline during the past year. No pneumothoraces were attempted in 1954, the second successive year in which none was established. Tuberculous empyema has become a rarity and no intrapleural pneumonolyses have been performed for two years.

Surgery. Pulmonary resection for residual cavitation and residual large necrotic tuberculous foci in the lung following six to nine months of conservative treatment with rest and chemotherapy has been applied at this sanatorium during the past year. However, with accumulating evidence regarding the effectiveness of long-term chemotherapy we have felt more confident in certain cases to regard such chemotherapy as definitive treatment without resecting small circumscribed residual necrotic tuberculous foci which in previous years we might have considered necessary to resect.

Duration of Treatment. In 1954 we have continued to prescribe long-term chemotherapy using concurrently three antimicrobial agents including isoniazid. At the present time for all patients with active tuberculous disease, chemotherapy is commenced shortly after admission (after a number of specimens have been obtained if possible for laboratory examination). This

chemotherapy is continued, and whether or not supplemented by surgical procedures, the patient is almost always sufficiently well clinically to be attending the dining room for three meals daily (full exercise) by the twelfth to fourteenth month after admission. If the prescribed duration of chemotherapy is for eighteen months, the patient continues in sanatorium on full exercise for approximately four to six additional months unless he or she can afford to purchase the antimicrobial agents and pay for the administration of streptomycin outside of sanatorium. During 1954 we would estimate that the *average duration of chemotherapy* prescribed for patients commencing on treatment during the year was approximately *sixteen months*.

Pulmonary Resection. The place of resection in the treatment of pulmonary tuberculosis now seems firmly established. Small isolated lesions are not excised as uniformly as they once were, and completely healed areas of former excavation are not resected as frequently to-day as formerly, probably because faith in triple chemotherapy is stronger than it used to be in streptomycin and PAS.

(*a*) To-day the commonest indication for excision therapy is apical tuberculosis, formerly regarded as ideal for thoracoplasty collapse, but now treated by resection of the apical and posterior segments of the upper lobe, and sometimes by larger resections. This has so reduced the number of thoracoplasties that in 1954 only 4 patients received this form of collapse, as against 80 patients who had resections (three of them being bilateral resections). It is true that thoracoplasty was also done in three patients simultaneously with upper lobectomy, and in five others to treat bronchopleural fistual or empyema following resection or decortication, but this is not collapse therapy as commonly defined. Of the 83 resections, 50 were for lesions requiring removal of less than one lobe.

However, a large number of resections continue to be done for the reasons that have been accepted for many years, viz.:

(*b*) Lower lobe cavity, especially after failure of artificial phrenic paralysis and artificial pneumoperitoneum;
(*c*) bronchial stenosis with atelectasis and caseation distal to it;
(*d*) tuberculous bronchiectasis with positive sputum;
(*e*) a limited lesion so situated as to be difficult to collapse without undue wastage of healthy lung;
(*f*) a tuberculoma of doubtful stability or larger than 2.0 cm. in diameter;
(*g*) destroyed lung, sometimes in the presence of empyema, when pleuropneumonectomy would be required;
(*h*) a lesion still active after collapse by a good thoracoplasty applied over a reasonable length of time (one year).